"NATURE", JUNE 24, 1961
SUPPLEMENT: RECENT SCIENTIFIC AND TECHNICAL BOOKS

# NATURE

*A Weekly Journal of Science*

Vol. 190, No. 4782 SATURDAY, JUNE 24, 1961 2s. 6d.

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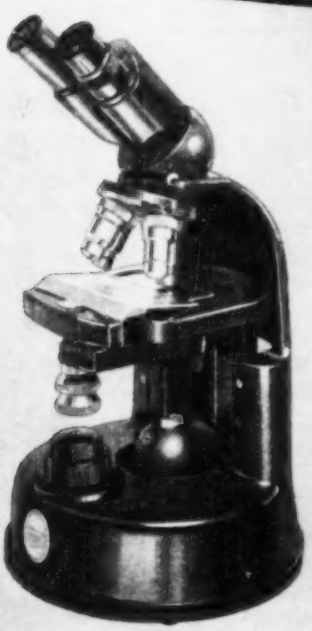

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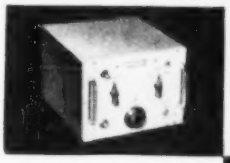

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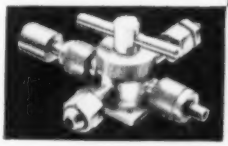

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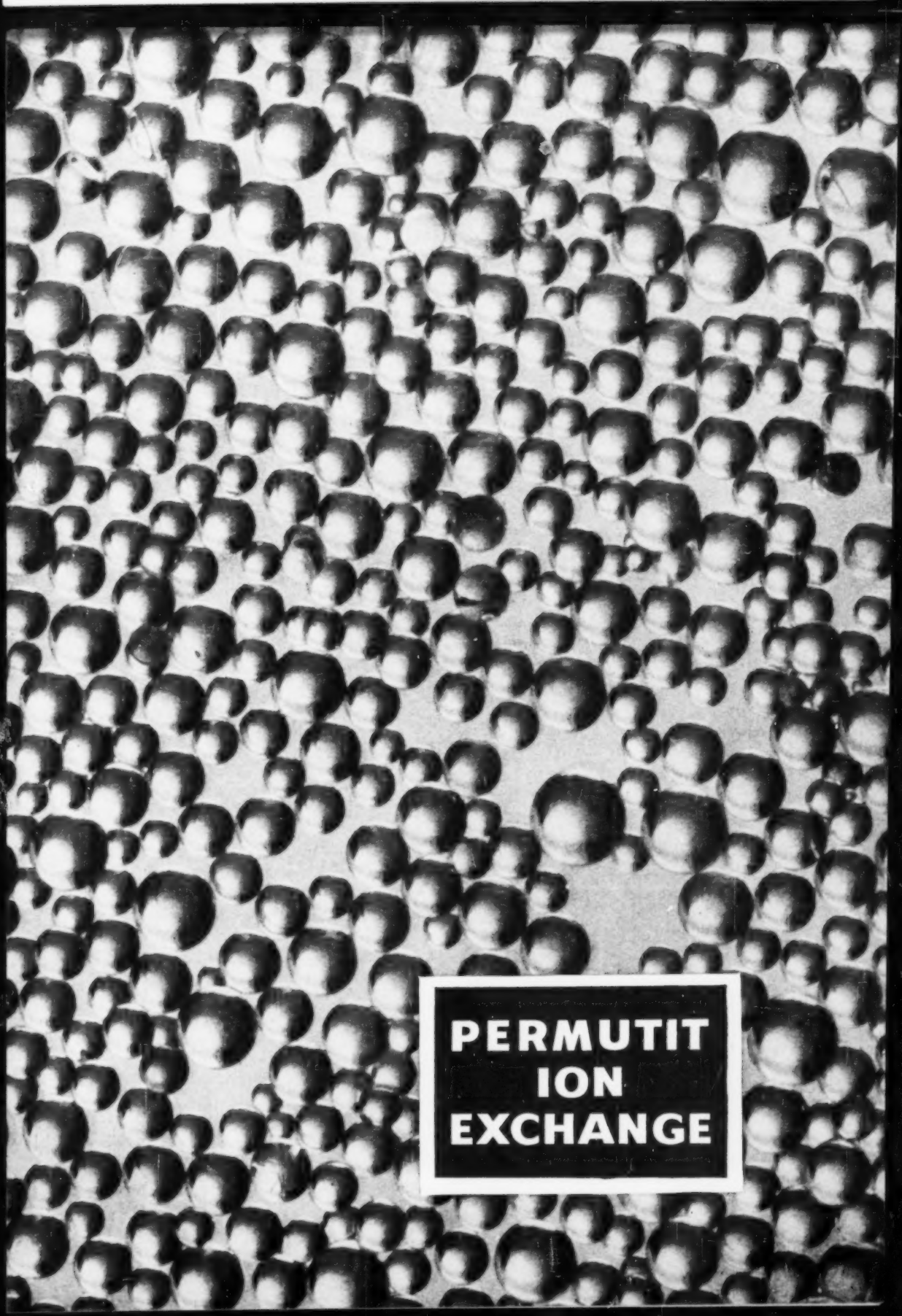
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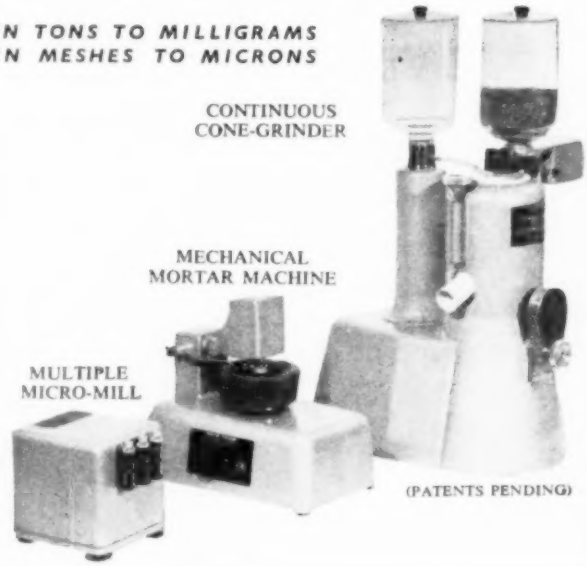


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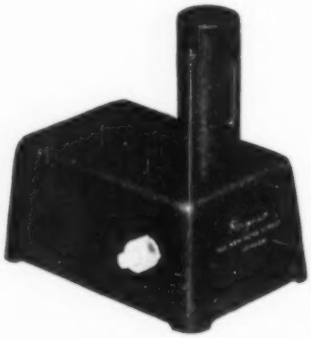

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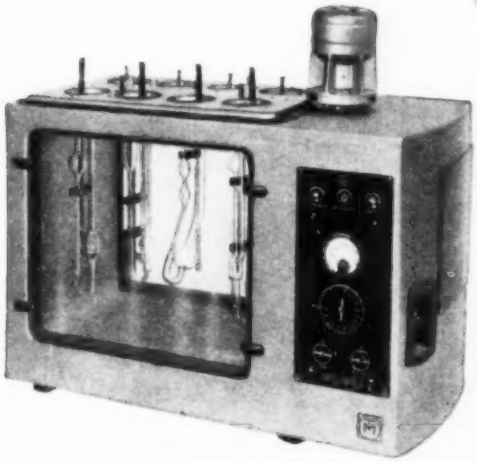

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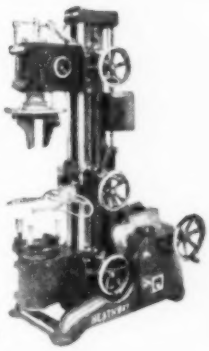

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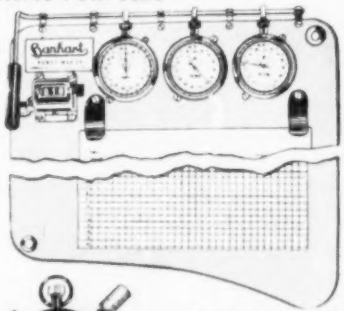

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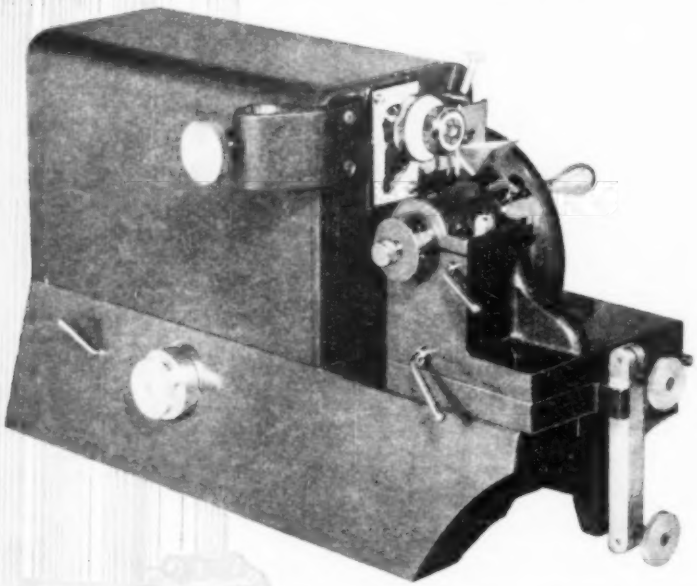

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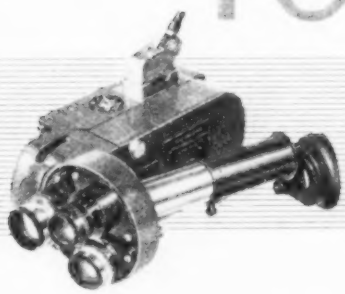

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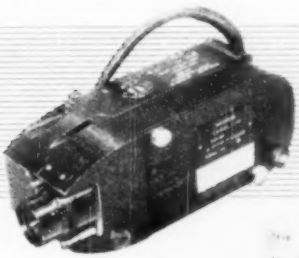

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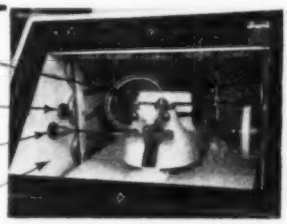


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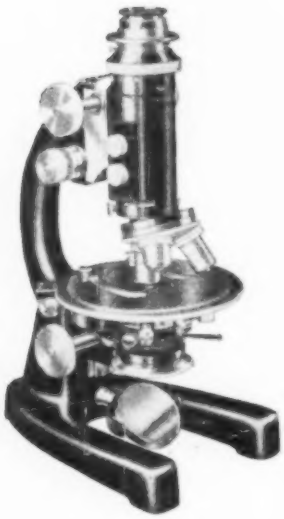

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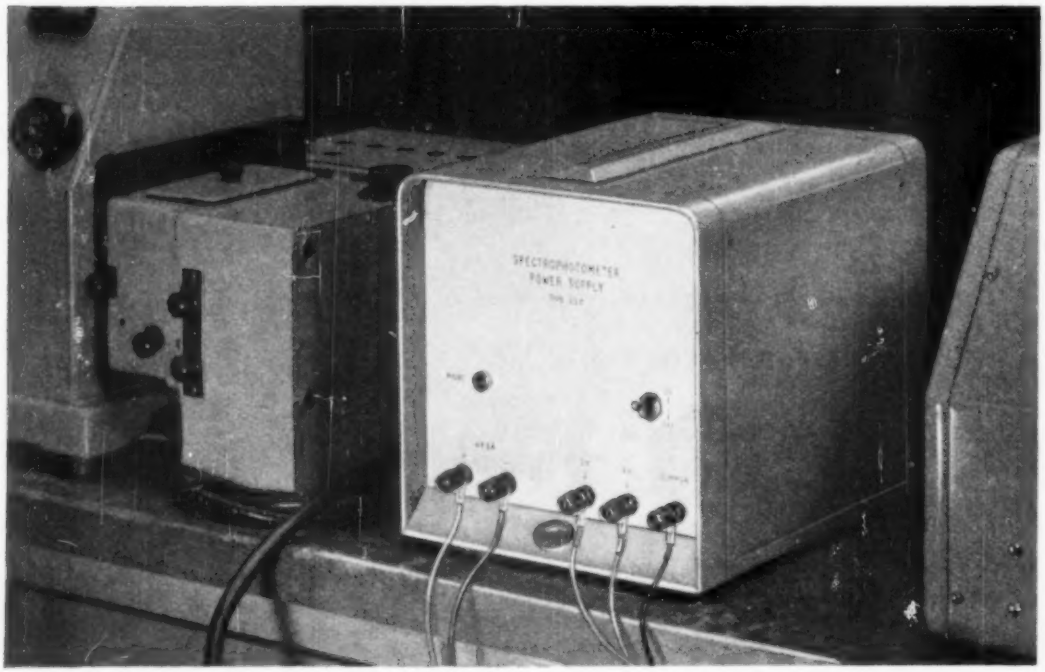

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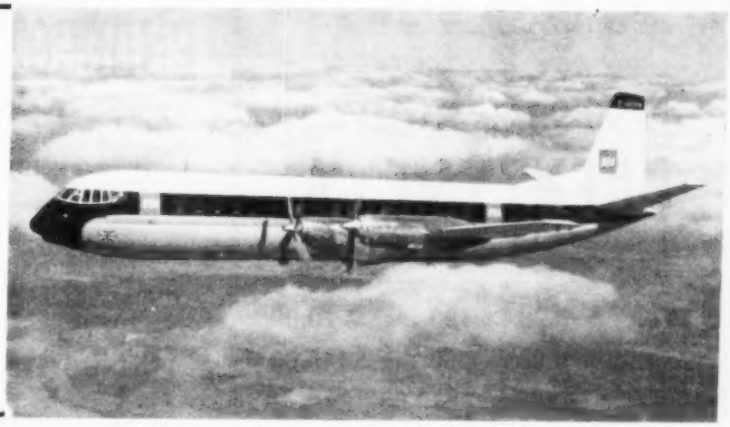

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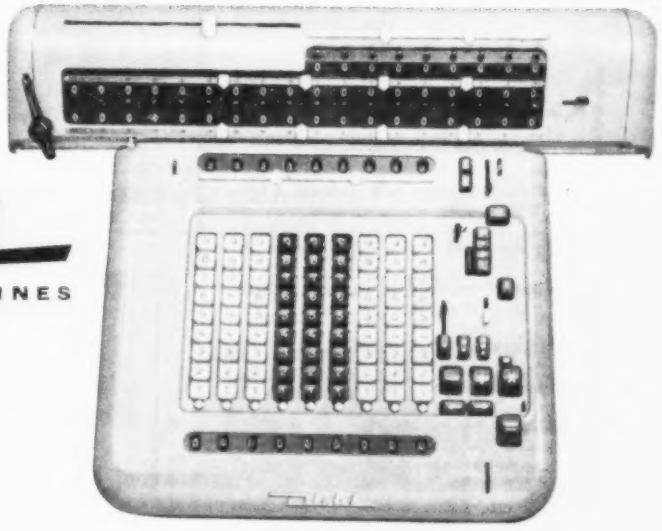

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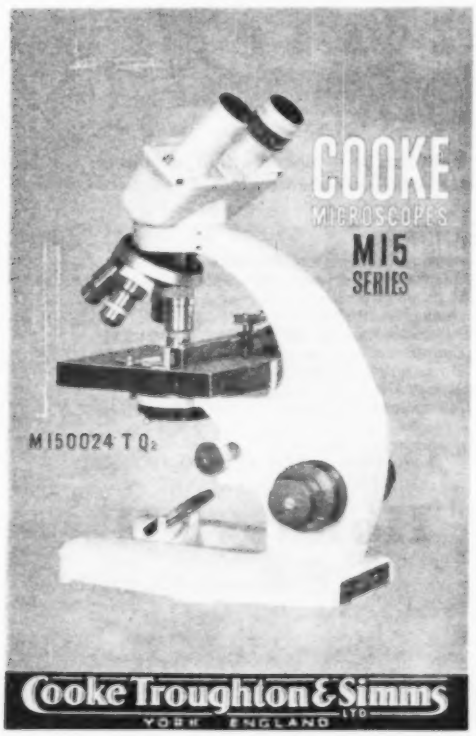


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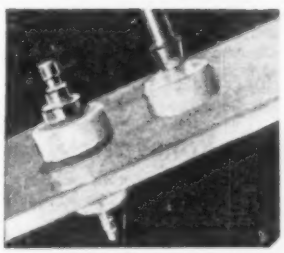

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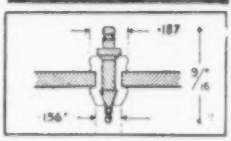


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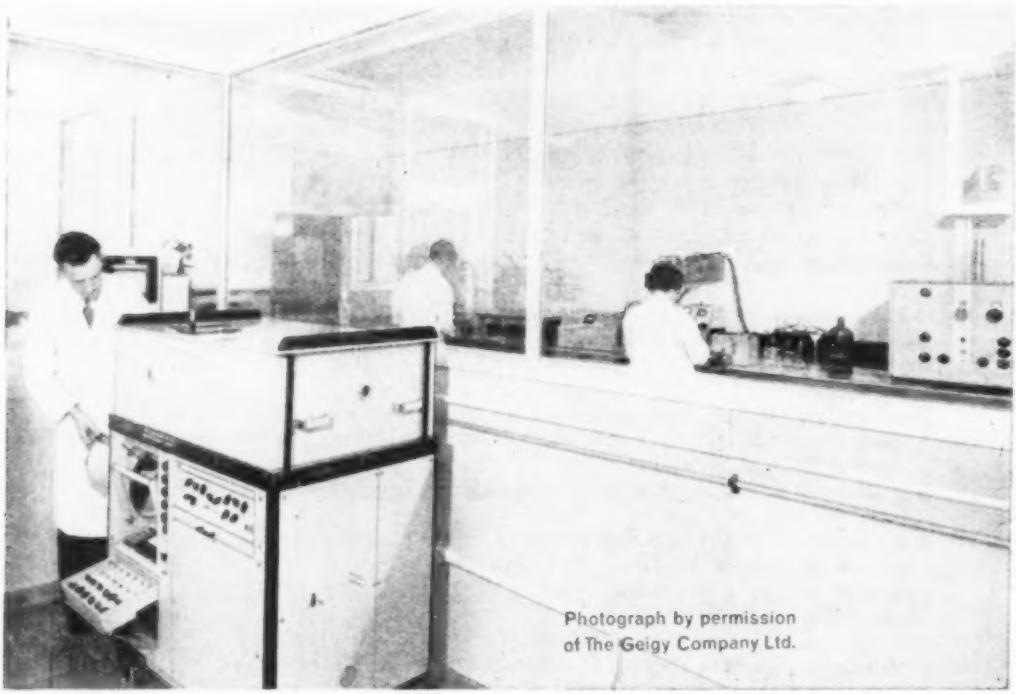

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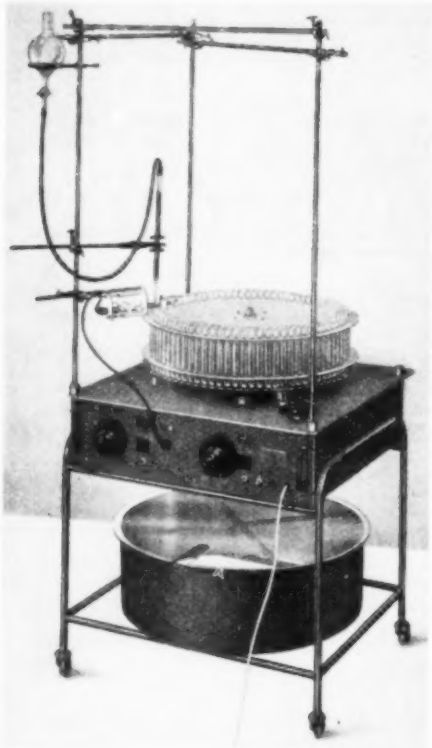

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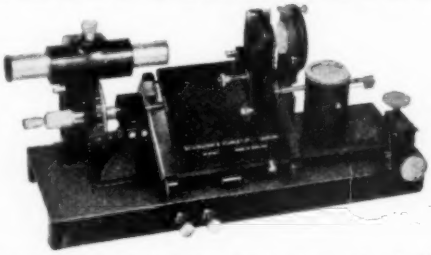

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# SCIENTIFIC AND TECHNICAL DEVELOPMENT IN PAKISTAN

IN January 1960 the Government of Pakistan appointed a Scientific Commission, under the chairmanship of A. K. Khan, to consider how best scientific research in the country, at present disjointed and scattered, could be promoted and integrated; ways and means for providing adequate facilities to the research organizations of the country and of ensuring the utilization of the results of their researches for the overall development of the country; and ways and means of making scientific careers attractive and comparable in prospects, emoluments and status to other services of equal national importance. The Commission was assisted in its deliberations by Prof. A. V. Hill and Dr. L. A. Jordan, Dr. F. T. Rosser, of the National Research Council, Canada, Mr. F. E. Nicholls, of the Australian Commonwealth Scientific and Industrial Research Organization, and Dr. S. Komagata, formerly chairman of the Japanese Atomic Energy Institute. Apart from an introductory chapter reviewing the importance of science to under-developed countries and Islamic contributions to science, which gives a timely reminder of the outstanding contributions Muslims have made to science, the Commission's report* follows the pattern of numerous other reports in this field in other countries. Reviews of the development of scientific organizations and of the tasks and problems for science in Pakistan are followed by chapters on a National Science Council, the establishment of which is recommended, on the organization of defence research, the careers and status of scientists, utilization of the results of research, and on facilities and resources for research.

Generally speaking, the recommendations of the Commission are in line with the policies that have been adopted in Great Britain and in the United States, and with the recommendations of the recent report, *Strengthening Western Science*. It is recognized, for example, that in view of the rapid industrialization of Pakistan and the programme of general economic development envisaged in the Second Five-Year Plan, it is necessary to accelerate scientific research in certain fields that have lagged behind. Emphasis is placed on strengthening scientific effort in the universities and the assumption of greater financial responsibility by the Government. It is also recommended that more attention should be given to research ability and the needs of research in recruiting staff; Western experience would suggest that the Commission goes too far in recommending that the promotion of lecturers, readers and professors in the Science Department should depend on the quality of their research. It is now widely recognized that one weakness in British universities is due to the failure to pay sufficient attention to teaching and organizing ability, and to the practice of giving undue weight to the amount of published work in appointments to university posts.

The Commission recommends that universities should be primarily concerned with fundamental research, leaving applied research to the Government-sponsored research councils. It suggests, however, a mutual exchange of personnel between universities and research councils; such mobility of research workers, as well as of academic staff generally, might with advantage be more encouraged in Britain. The subjects noted as comparatively neglected in Pakistan's universities at present and requiring greater attention include the biological sciences, biophysics and biochemistry, geology, mining, astronomy, metallurgy and chemical engineering.

Of the administrative structure of Government departments, the Commission is highly critical. Apart from recommending considerable decentralization and study of the possibility of creating a separate Scientific Service, the Commission found considerable duplication of activities of the provincial and central Government departments, and that the administrative and executive heads of scientific departments were exercising control over teaching and research institutions which was detrimental to efficiency. Such teaching and research institutions should either be autonomous or linked up with universities. In particular, reconstitution of the Agricultural Research Council and the Medical Research Council is recommended; the Council of Scientific and Industrial Research should reorganize its laboratories and research division so as to conserve the limited scientific man-power available and should devote greater attention to major problems of consequence to the national economy, as well as initiate a co-ordinated programme for training research workers. The Atomic Energy Council, besides intensifying its own training programme, should establish an Institute of Nuclear Sciences and Technology. The Commission also advocates the formation by industries of co-operative research associations which should be subsidized by the Government.

The research organization visualized by the Commission, outside the universities and Government departments, comprises the five councils already mentioned, together with the Council for Works and Irrigation Research and a National Science Council

* Government of Pakistan: Ministry of Industries. Report of the Scientific Commission of Pakistan. Pp. iv + 102. (Karachi: Ministry of Industries, 1960.)

with purely advisory and co-ordinating functions located in the President's Secretariat, and responsible either to the President or to a Minister designated by him. The Research Councils, which should be autonomous bodies, attached to the respective Ministries of the central Government, should establish research institutes and laboratories in different parts of the country, while defence research should be entrusted to an independent organization under the Ministry of Defence, headed by a scientific adviser, and with a Defence Science Liaison Committee with the chairman of the National Science Council as chairman to maintain close liaison with the National Science Council. The Defence Science Organization should be entitled to place contracts with any of the Research Councils for the solution of specific problems.

As regards the programme for science in Pakistan, priority is given to the food problem; but this is not conceived simply in terms of extending and intensifying agriculture. It embraces also research on the utilization of plant material and on improving the nutritional value of food crops. In the field of irrigation, problems concerned with waterlogging, subsoil structure, soil mechanics, rate of water-flow, de-silting, dredging and bed-lining of canals call for intensive research, and there are the special problems of de-salting sea-water and conservation of subsoil water resources involved in irrigating the arid zones of West Pakistan. Cheap electric power, however, is a pre-requisite for the development of agriculture and irrigation, as of industry and communications, and the Commission recommends raising the consumption per head of electricity within the next thirty years from 30 to 400 units, a figure which is still only about half the present consumption in Japan. The upgrading of mineral ores, the various aspects of fibre technology and the utilization of indigenous raw materials all offer great opportunities for scientific and technological research to contribute to the development of Pakistan. Attention is also directed to the serious problems in the field of public health, including the eradication of epidemics and control of preventable diseases, the investigation of diseases peculiar to Pakistan, to family planning and birth control, and to nutrition. These may require tackling in special institutions, and finally the Commission recommends the establishment, attached to a university, of an institution where modern statistical methods of sampling can be investigated.

The Commission recognizes that utilization of the results of research requires special attention, and in agriculture it makes a number of specific suggestions for establishing co-operation between research workers and those engaged in extension services and securing the co-operation of farmers. As regards industrial development, it recommends that processes developed by the Council of Scientific and Industrial Research which call for heavy investment should be handled by the Pakistan Industrial Development Corporation, and that where exploitation is undertaken by private industrialists, foreign exchange should be released for import of the machinery and raw material required. It also recommends the organization by the Council of Scientific and Industrial Research of an Industrial Extension Service with the view of publishing and disseminating information on the latest techniques and processes.

It is interesting to read these specific recommendations for Pakistan in the light of the papers on science and the new States which occupy the greater part of the February 1961 issue of the *Bulletin of the Atomic Scientists*, more especially those by Principal W. A. Lewis and Prof. E. Shils. Principal Lewis points out that the primary need of the new States is not the development themselves of new knowledge but the application of existing knowledge to their problems, and especially the devising of new technologies which will make man-power much more efficient without much capital—a point on which both Lord Fleck and Prof. P. M. S. Blackett have already laid some stress. Principal Lewis devotes most of his paper to this question of man-power, stressing the critical importance of secondary education and the need for political leaders to give priority to economic development and the factors which promote it. Although he writes rather pessimistically about this point in general, the fact that the Pakistan Government has already indicated its intention of implementing the recommendations of the Science Commission's report shows that in that country at least there is the will to seek new ways of progress.

On the financial aspect Principal Lewis has little to add, but stresses once more the importance of political stability, in order to attract technical assistance and to use it wisely and productively. Prof. Shils, discussing scientific development in the new States, is concerned more particularly with the conditions required to foster research and training in science and technology, and likewise stresses the importance of secondary education, as well as the major dependence of technological and scientific research in such States on Government policy and support. Of specific fields of research he only mentions the importance of the prospecting and appraisal of resources, and of work directed to the adaptation to new circumstances of industrial or agricultural processes already used in other countries. He notes, however, the impracticability of planning fundamental research, or even technological research, from a central position, and his paper largely discusses the policy and organization required to create the appropriate conditions of scientific work in laboratories and universities. So far as organization is concerned, his suggestions fully support the recommendations in the report from the Scientific Commission of Pakistan, and that is also largely true of the recommendations relating to the careers and status of scientists and those facilities and resources for research contained in the fourth and eighth chapters of the Commission's report. One comment might here be made in respect of both Principal Lewis's and Prof. Shils's observations about fundamental research: while undoubtedly it would be unwise for the new States to devote more than a minor effort to such research, some such research has its place both in attracting creative workers to a

scientific career and in providing the stimulus of participating in scientific advance generally. Such factors are sometimes more important than remuneration, on which the Commission reasonably enough lays a good deal of stress. Conditions in Pakistan are, in fact, so poor that the Commission makes detailed recommendations for the creation of a Pakistan Science Service, and specific salary scales are recommended for scientists and technicians employed by the Research Councils. There are recommendations regarding the ratio of scientific to supporting staff which, while intended to increase the proportion of scientific staff, do not seem to take account of the number of supporting technicians required to make effective use of the scientists and technologists. Some attention is given to the question of status, and Government support of scientific societies is recommended; but generally the report is a good way behind the recommendations of the Barlow Report on scientific staff in Britain published in 1945.

To overcome the existing shortage of scientific and technical man-power, the Commission advocates a massive training programme to be entrusted to the National Science Council, which will be responsible for co-ordinating the requirements of the various Research Councils. The programme contemplates sending abroad at least a hundred talented science graduates each year for intensive training during the next five years, the establishment of two big training centres, one in East Pakistan and one in West Pakistan, for training technicians in glass-blowing, precision tool-making, high-vacuum maintenance and the like, while import duties on scientific instruments and apparatus, laboratory chemicals and furnishings should be waived until manufacturing capacity is developed within the country. Similarly, to facilitate the import of scientific books and technical periodicals and the equipment required to maintain scientific laboratories, the universities, selected scientific departments of Government and the Research Councils should be granted an 'individual general licence' which they could operate freely. Establishment of branches at Lahore and Dacca of the Pakistan National Scientific and Technical Documentation Centre is recommended, while the Commission also recognizes the importance of training librarians and offering them an attractive career.

The Commission has clearly taken a most comprehensive view of Pakistan's needs, and stresses some factors to which little attention has yet been given in Government quarters in Britain. It visualizes the allocation to this scientific effort of at least 2·5 per cent of the national budget. Principal Lewis estimates that most under-developed countries need to provide about 25 per cent of the national output to promote economic growth at the rate of about 4 per cent per annum, of which about half is required for capital formation and half to supply an adequate framework of public services—3 per cent for education, 2 per cent for public health, 3 per cent for communications, agriculture and geology, and about 4 per cent for general administration and welfare. Actually, in most such countries only 15 per cent of the national income is available for the public services and capital formation together; but Principal Lewis takes an optimistic view of the prospect of providing the necessary saving from taxation.

However that may be, the report of the Scientific Commission of Pakistan shows as clearly as the papers in the *Atomic Scientists Bulletin* how large a contribution science can make to the development of new States, and the opportunities for the scientist or technologist to assist the process. These papers add little to our knowledge of the conditions in which technical assistance can be most effective; but in emphasizing the conditions in which scientific work can flourish, they point to the value of the interest and support of the scientific community. When Prof. Blackett writes of the need for a greatly increased international effort and the co-operation of such organizations as the World Health Organization and the Food and Agriculture Organization, or of the primary need to understand the problems and difficulties of the emergent countries and appeals for more men and money from the more affluent countries, he is unlikely to be overlooking the way in which the scientists and technologists of Britain and other advanced countries can help to create the conditions in which such assistance is effectively used. The association with the Scientific Commission of Pakistan of Prof. A. V. Hill and Dr. L. A. Jordan from Britain, of Dr. F. T. Rosser from Canada and Mr. F. E. Nicholls from Australia, illustrates one way in which help is given. It can be given all the time, however, not only in response to such specific requests, but also in the continuing contacts between scientists and technologists in Britain with those of the under-developed countries at present in British universities and colleges of technology—now perhaps some 50,000—in the interchange of visits in many different ways, in the Overseas Scientific Service and the expanding programmes of the Commonwealth Education Conferences. These opportunities were emphasized by several speakers in a debate in the House of Lords on February 22. Only perhaps as such opportunities are used to the full can the vital task of educating the Governments of these countries to the full understanding of the conditions in which science and technology flourish be fully discharged. The report of such a Commission as the Scientific Commission of Pakistan is only a beginning. Its implementation requires public understanding as well as the co-operation of scientist, technologist and administrator in countries where such collaboration has scarcely begun; and the declaration, unanimously accepted by the Rehovoth Conference last summer, which Abba Eban describes in his article "Science and the New States" in the *Bulletin of the Atomic Scientists*, fittingly urges the scientists of advanced countries to become more pre-occupied with the problems facing newly developing communities, and to advise the Governments of new States to include the establishment of a scientific tradition and practice among their early targets.

# ATOMS AND ELECTRONS

## Quantum Theory of Atomic Structure

By Prof. John C. Slater. (International Series in Pure and Applied Physics.) Vol. 1. Pp. xii + 502. 85*s*. 6*d*. Vol. 2. Pp. ix + 439. 101*s*. (New York: McGraw-Hill Book Company, Inc.; London: McGraw-Hill Publishing Company, Ltd., 1960.)

IN 1933, only seven years after the introduction of wave mechanics, Slater and Frank published their *Introduction to Atomic Physics*. They allotted 200 pages to atomic structure. But in 1951, when wave mechanics was just 25 years old, this material had grown to a complete book, *Quantum Theory of Matter*, with 500 pages. To-day, in 1961, Prof. Slater takes the first half of this second book, and expands it into two full volumes totalling nearly 1,000 pages. This is a striking indication of the almost catastrophic way in which our knowledge of this field has developed.

But the field itself has spread. Atomic theory is no longer the province of the spectroscopist measuring line frequencies and line widths. It plays a fundamental part in the totally new field of molecular structure, and its ideas have taken root in much of nuclear structure and the most exciting of all modern branches of theoretical physics—the solid state.

The subject is ripe for a major exposition. It seems likely that most of the main results and theories are now known. The advent of electronic computers has already influenced techniques. Much remains to be studied, but the methods of doing this are now fairly clear. It is entirely appropriate that Prof. Slater should write this monumental work. For during the past fifteen years his group at the Massachusetts Institute of Technology has studied atoms, molecules and solids with great success. We are now promised further books on these other topics. If they match the present ones in excellence they will be very welcome indeed.

Here is effectively everything that matters in the theory of atomic structure. It is set out in Slater's lively style (sometimes almost too colloquial), and with very great assurance. Reading these volumes is like watching a first-class chess player march irresistibly to his object. There is complete mastery of the material, much of which is his own, and a complete certainty about its ordering.

The first volume starts with 160 pages recapitulating elementary wave mechanics. Despite the author's claim, I do not feel that this is suitable for a beginner: it is inevitably compressed. But it is excellent for a student who already has some knowledge. Then follow accounts of the hydrogen atom, self-consistent-field, angular momentum, multiplet structure, with application in the iron group, and a series of some twenty appendixes elaborating points inadequately covered before. This material is enough to understand the main lines of thought, but not sufficient to start research.

Volume 2 starts with Hartree–Fock theory, and then goes on to group theory, angular momentum operators, Racah's method for complex spectra, the Dirac theory, magnetic properties of complex atoms, transition probabilities and hyperfine structure. It contains a wonderful set of tables, and carries the subject right up to the present day. Both volumes are enriched with a series of bibliographies that greatly enhance their value.

Comparison is inevitable with Condon and Shortley's *Theory of Atomic Spectra*. In Slater there is much less direct comparison with experimental data, and more 'drive' towards the basic theory: there is almost nothing about *jj*-coupling (this is a pity) and isotope effects, or about polarizability and Stark effects. But there is the first full-scale development of Racah's work, the use of projection operators, the Fermi hole, nuclear quadruple effects, none of which is found in Condon and Shortley's book. Numerical techniques are also more advanced, and the whole outlook is more modern.

No one can expect to be entirely satisfied. But I found only one minor mistake. I could have wished for more reference to the Thomas Fermi statistical method, and a better account of Hund's rules (Hund does not get quite his share of credit). I also wish that the Rydberg unit of energy had been replaced by the atomic unit, so that a self-consistent set of units could be used. But these are relatively trivial. Here—without any doubt at all—is a definitive account of atomic structure. It is a magnificent work, which no one but Slater could have written; and it is beautifully published.

C. A. Coulson

# PROBLEMS OF ECONOMIC AND SOCIAL DEVELOPMENT

## Jamaica, 1830–1930

A Study in Economic Growth. By Gisela Eisner. Pp. xxiii + 399. (Manchester: The University Press, 1961.) 50*s*. net.

THE publication of this work can be welcomed without reservation by all who are interested in the problem of economic and social development. The investigations on which it is based were initiated and guided by Dr. Arthur Lewis, when professor of economics in the University of Manchester, and it thus provides evidence of the growing sense of responsibility of the new West Indian middle classes for the welfare of their communities. The project is as ably conceived as it is brilliantly executed.

Our knowledge of economic growth and social change has hitherto been severely restricted by the scarcity of accurate studies of the history of the societies which have been subject to the most rapid development over the past century. Here is one more, and a very good one, to add to our small collection. The author has extended her work over a wide field; she has thus been able to show how economic growth and organization have been interrelated with the social structure and social history of Jamaica. The result is to give the book a much wider interest than a more restricted study of economic statistics and economic trends would possess.

It would have been even more helpful if the period covered could have been extended to 1943, a year in which an elaborate census provided much material which could have been used for purposes of general comparison with the situation which prevails to-day. Even though the data were somewhat affected at that time by the impact of the Second World War, this was not so important as might be supposed; the influence on economic and social life of the post-war period of planned economic development has been made more profound. It is probable, therefore,

that 1943 will in the future be regarded as the end of the old era of colonial policy, rather than the start of the new period of democratic self-government. One thus hopes that Mrs. Eisner's work will be used as the basis for further studies by Jamaican economists. It will serve this purpose admirably.

T. S. Simey

## ORGANOMETALLIC CHEMISTRY

### Organometallic Chemistry

Edited by H. Zeiss. (American Chemical Society Monograph Series, No. 147.) Pp. xiv + 549. (New York: Reinhold Publishing Corporation; London: Chapman and Hall, Ltd., 1960.) 140s. net.

THE enormous output of work within the broad definition of organometallic chemistry fully justifies the production of this monograph.

The ten chapters, occupying 528 pages, consist of "a series of research subjects which are under active investigation—at the present time—by their respective authors". The book is intended primarily for graduates and the more advanced chemist. The subjects and authors of the chapters are: carbon-metal bonding, James W. Richardson; benzyne chemistry, Rolf Huisgen; vinyl-metallics, H. D. Kaesz and F. G. A. Stone; organoboranes, Herbert C. Brown; organo-aluminium compounds, Karl Ziegler; organo-silylmetallic chemistry, Henry Gilman and Hans J. S. Winkler; cyclopentadienyl metal compounds, P. L. Pauson; arene complexes of the transition metals, H. Zeiss; transition metal alkyls and aryls, G. E. Coates and F. Glockling; metal carbonyls and related compounds, J. Chatt, P. L. Pauson and L. M. Venanzi.

In Chapter 1 a modern qualitative treatment by molecular orbitals of the carbon–metal bond is given. An introductory molecular orbital description of the $HeH^+$ molecule is extended rather rapidly to some specific metal cyanide, carbonyl and cyclopentadienyl complexes. This specialization is intended to "demonstrate and catalogue the variety of interactions present in metal–carbon bonds in detail" rather than review a broad range of compounds. A final discussion of the stability of alkyl and aryl transition metal complexes is complementary to the theoretical discussion in Chapter 9. The thorough review of the very recent benzyne chemistry is decidedly more 'organo' than 'metallic' and its inclusion in this monograph emphasizes the wide scope of organometallic chemistry. A competent systematic coverage of vinyl metallic chemistry complementary to recent reviews is given. The infra-red spectra of a number of vinyl substituted compounds are reproduced and the group characteristic patterns clearly shown.

The chemistry of organoboranes has also been reviewed recently and therefore the emphasis in this work is laid on the most up-to-date advances, and on new synthetic procedures. The hydroboration reaction is discussed in considerable detail and the great familiarity of the author with this field is evident.

Nearly 400 references including a large number to patent literature demonstrate the importance and extent of organo-aluminium compounds. As would be expected, there is an authoritative coverage of the synthesis and classification of these complexes by K. Ziegler. This is followed by a discussion of their molecular structure and properties. The necessarily limited size of one chapter has resulted in rather a compromise between useful detail and generalizations.

Organosilylmetallic chemistry is a field which surely must expand rapidly in the next few years, particularly where transition metal chemistry is concerned. The few organosilyl transition metal complexes which have already been reported are, however, not mentioned in this review. Detailed preparations of the alkali-metal derivatives are given and their reactions are described. This chapter does not make very exciting reading. The division of the so closely interrelated fields of aromatic, carbonyl, and alkyl and aryl transition metal complexes into four chapters, under different authorship, has resulted in a good deal of confusion as to who should write what about which. In the attempt to avoid duplication with recent reviews and with subsequent chapters, the topic of cyclopentadienyls is given a fragmentary treatment. The aromatic ring substitution reactions are, however, summarized and some useful reaction schemes are given.

A historical approach to arene complexes is developed into a concise survey of the known examples which are given in a seven-page table. Non-benzenoid arene metal complexes are briefly considered. The acetylenic synthesis by cyclic condensation of arene compounds is discussed, as is also the mechanism of the Job–Cassels reaction.

Chapter 9 on transition metal alkyls and aryls is largely culled from the book on *Organometallic Chemistry* which is written by one of the authors of this review. Insufficient progress has been made in this field in the few months separating the appearance of these two books to warrant this duplication. The topic is well and more extensively covered in the original book.

Finally, Chapter 10 consists of a rather limited review of metal carbonyl and related compounds. The most recent and important developments are, however, considered and more than 300 references are given.

The book has an author- and subject-index and is excellently produced. On the whole a useful book but unfortunately rather expensive.

M. L. H. Green

## THEORIES OF CARCINOGENESIS

### Carcinogenesis

By I. Hieger. Pp. xi + 138. (London: Academic Press, Inc. (London), Ltd.; New York: Academic Press, Inc., 1961.) 35s.

DR. HIEGER'S principal theme is "the putting into perspective of the theories which have been advanced to interpret the process whereby normal cells and tissues are transformed into cancer". Except for one chapter in which the main types of cancer-producing agents are described, and their effects on various tissues illustrated by experimental records, the book is devoted to the consideration of the most important theories which have been advanced to explain the carcinogenic process in general. It is in the bringing together in one place of critical accounts of these various theories that the main value of the book lies.

Hieger analyses them with refreshing candour and no undue respect for persons. His criticisms merit serious attention. The evidence on which cancer theorists rely is often equivocal and always incom-

plete, but it must be remembered that criticism necessarily rests on a re-interpretation of the same data. For example, Hieger uses the "multicentric view" of carcinogenesis to support his attack on the somatic mutation theory. He argues that the observed multicentric genesis of tumours in a region of tissue undergoing carcinogenic stimulation requires that all or almost all the cells in the region should mutate, and that this is numerically impossible given the known mutagenic capacity of effective doses of carcinogens. But it is pre-cancerous changes which are regional, that is, appear to affect all cells in a treated region (as Hieger points out in one place, but ignores in his argument); tumours arise at relatively few points within the region. The number of cells in which the definitive neoplastic change (whatever that is) occurs may be only a minute fraction of those at risk.

One might pick out other instances of this kind, but they would not invalidate Hieger's main theme—the unsatisfactory state of cancer theory to-day. That is undeniable, and, indeed, to survey the divergence and mutual incompatibility of rival theories of carcinogenesis is a chastening experience. But I doubt if it is reasonable or wise to demand, at this stage, that they should be consistent and generally applicable. Most fruitful hypotheses have started with a strictly limited application; inconsistencies were disregarded for a time and eventually explained, and in the meantime experiment and speculation were stimulated.

A frequent complaint of Hieger's is that theories of carcinogenesis are "tautologous". For example, he quotes the following passage of Burnet's: "In many ways it (carcinogenesis) resembles the evolutionary process among free-living organisms. Change in Nature results from the appearance of mutations, from their phenotypic expression in various combinations, and from the selective action of environmental factors in ensuring the survival of the fittest. In the body the cancer cell has an undoubted short-term survival advantage over normal cells and in a sense we can look at it as representing a clone, which, by processes formally equivalent to mutation, has developed a gross advantage in proliferation within the existent internal environment of the body". Hieger's comment is: ". . . Sir Macfarlane has only said: 'An advantageous mutation confers an advantage'—a tautology which does not assist us in understanding carcinogenesis". I do not think this type of criticism is well directed. Opinions differ as to whether Burnet has drawn a valid comparison; but it must be remembered that what he and some other theorists are trying to do is to show the formal equivalence of carcinogenesis to other processes in Nature which are better understood, or for which there are, at any rate, generally accepted explanations covering wide fields of fact. They attempt this by making assumptions, in line with other evidence, from which the known facts of carcinogenesis can be deduced. The steps of such arguments are certainly tautologous, but only in the sense that all mathematics is tautology (as some in fact maintain).

There is much more to be learned from these theories than appears from a catalogue of their inadequacies, real or apparent, and I hope that the readers of this book will not be prevented by the author's scepticism from studying them.

When reading or listening to a severe critic of the theories of others it is natural to look forward to the moment when he will introduce a theory of his own, in order that we may give him a taste of his own medicine. Dr. Hieger does not fall into the trap. Since he believes that all present theories of carcinogenesis are inadequate he is surely wise in not adding to their number. He indicates, however, what he regards as the most hopeful directions for future work, some of which have received less attention than they deserve. In his last paragraph he states his opinion that "the most hopeful approaches to the solution have not been from a theoretical direction but by a more modest and empirical route". His own important contributions to the study of carcinogenesis have been made chiefly by the latter method, and many experimental pathologists, whether or not they endorse his strictures, will agree with his conclusion.

M. H. Salaman

## THE PROBLEMS OF AGEING

### Man against Aging

By Dr. Robert S. de Ropp. Pp. v+310. (London: Victor Gollancz, Ltd., 1961.) 21*s*. net.

ONE of the results of medical advances in the past hundred years has been an increasing proportion of elderly people in the population, and the public is becoming increasingly aware of and interested in the new medical and social problems which these changes are creating. *Man against Aging* is intended to provide them with the sort of information about old age which they have grown accustomed to receiving in other branches of medicine.

To get the basic information and attitude over to lay readers requires special techniques and unusual gifts from an author and perhaps modified standards of criticism from a reviewer. The start of this book is not at all encouraging, for it contains a collection of the various fanciful notions that have accumulated over the centuries, interspersed with vaguely salacious remarks and unwarranted, and irrelevant, side-cracks at the standards of biological science in communist countries. One assumes that this is intended to persuade someone who picks up the book to go on reading, and having got it all off his chest the author settles down to a very reasonably accurate assessment of the present state of our knowledge about the ageing process, our difficulties in defining it, how it affects different forms of animal life and different parts of the body, and how we are trying to analyse the process and decide whether there is a specific cause of ageing or not. After dealing with these gerontological problems the author goes on to the geriatric aspects and describes the common serious diseases of the latter part of life. Once again his reading of the specialist literature seems to have been wide and his assessment not at all extravagant. The last part of the book is entitled "The Art of Aging". This part, which boils down to a recommendation to old people to keep on working, is less successful perhaps because the social science side of gerontology is less well developed than the biological side.

Once one has discounted the jargon and lavish use of adjectives that it is apparently necessary to introduce into any popularized account—the incredibly complex, the ceaseless stream, the wealth of vital chemicals and so on—one can recognize in much of this book a successful attempt to make the reader aware of the problem and our present position of ignorance in ways which can only be helpful.

P. L. Krohn

# CARL NÄGELI AND THE FINE STRUCTURE OF LIVING MATTER*

By Dr. J. S. WILKIE
Department of the History and Philosophy of Science, University College, London

THE status of Nägeli as the founder of a new branch of biological science has been very generally recognized. Among his contemporaries, we find Sachs, Hofmeister and Pfeffer speaking in terms of the highest admiration of his work in this field; and among workers in the present century Seifriz, Meyer and Mark, Preston and particularly Frey-Wyssling, seem to be in no doubt that he was the first to obtain results of value in the study of fine structure.

Prof. A. F. Huxley, in his inaugural lecture delivered at University College, London, has pointed out that the work of Brücke on the fine structure of muscle has been confirmed in important respects by recent studies. Brücke was a contemporary of Nägeli, who refers to his work on muscle, and if the title of 'founder' were to be awarded simply for brilliance or originality it would be difficult to decide to which of the two it should properly be given. By this criterion there might, indeed, be others entitled to claim the title. However, just as we rightly award to Darwin the honours due to the founder of evolutionary studies, because of the extent of his labours and the cogency of his arguments, so do we, I think, appropriately assign to Nägeli the status of founder and originator of studies in fine structure.

I have for some time been engaged in studies intended to supply answers for the following two questions: (1) What exactly was the nature of the original contribution to biology made by Nägeli? (2) By what processes of observation, experiment and ratiocination did he produce the most original part of his work? To such historical questions it is scarcely possible to offer final and complete answers, and certainly the answers which I shall suggest here are not intended to be more than tentative.

It seems reasonably certain that Nägeli's work in this field was original in the three following respects:

(1) He appears to have been the first to appreciate the great and universal importance of what are now called high polymers—their importance, that is, in the fine structure of living things. Pfeffer[1] goes so far as to assert that Nägeli employed the concept of higher-order molecules, that is, of polymers, at a time when it was 'unknown to chemistry' ("zu einer Zeit . . . als die Chemie meines Wissens Molecülverbindungen als nähere Körperbestandtheile noch nicht kannte"); this is not strictly correct, for the possible existence of higher-order molecules formed by the union of many similar or identical unit-molecules was suggested by Berzelius in 1827 [2]. It seems, however, only reasonable to accept the testimony of Pfeffer that the notion was not widely known or widely accepted among chemists at the time when it was successfully applied by Nägeli. It is in any event certain that Nägeli owed nothing to Graham in this respect, for Graham's suggestion that "colloid molecules may be constituted by the grouping together of a number of smaller crystalloid molecules" appeared in a paper of 1862 [3], whereas Nägeli had formulated his hypothesis fully in his monograph on starch-grains, published in 1858 [4]. It seems to me probable that the idea of polymerization was in the air, as a mere notion without much empirical substance, during the 'fifties; but, if so, it is certain that Nägeli was among the first to make use of it and to give it the empirical substance which it lacked.

(2) Nägeli seems to have been the first to appreciate the presence and importance of a variety of cohesive forces in the structure of living matter at the molecular level. That this idea was in itself very original I cannot assert, though I believe it was; but the empirical observations by which Nägeli sought to establish it, and the arguments drawn from these observations are, I think, among the most original, as well as the most lasting, of his contributions. I describe this as a 'lasting contribution' because it seems to be a vague perception of what is more precisely formulated in, for example, the theory of *Haftpunkte*[5].

(3) A final original and lasting contribution is his discovery (for here we may use this dangerous word) of microcrystals or submicroscopic regions of lattice order in starch-grains and in the walls of plant-cells, together with the extensive development of his theory of the universal presence of such structures in plant-cell walls.

For the sake of completeness it will be as well to quote here Nägeli's formulation of his set of hypotheses concerning the structure of 'organized materials', by which he meant the structured parts of organisms, as contrasted with, for example, blood-plasma or cell-sap. In this passage[6], which belongs to the middle period of his activity, he is still using an old terminology, in which it was usual to call molecules 'atoms', so that he is able to use the term 'molecule' to designate his polymer-particles. This usage will be more readily grasped if it is remembered that the 'atoms' mentioned in this passage are 'atoms of starch', or 'atoms of cellulose', or even 'atoms of albuminous material'.

"Organized materials consist of crystalline, birefringent molecules (themselves consisting of very many atoms), which lie freely, but with a definite regular arrangement, alongside one another. As a consequence of preponderating attraction, each is surrounded in the moist state by an envelope of water; in the dry state they touch one another. Hence there are in organized materials two kinds of cohesive force: one unites the atoms to form molecules, in the same manner as they unite in general to form crystals; the other unites the molecules."

In his later writings, Nägeli calls his crystalline particles *Micelle*, or *Micellen* (for, *in unkonsequenter Weise*, as Prof. Frey-Wyssling says, he used both forms of the plural), a word which has passed into English as (still considering the plural) micelles or micellæ.

Fig. 1 shows, above, one of the two figures given by Nägeli to illustrate his concept of micellar structure; and, below, a diagram published in 1929 by the late Prof. Seifriz (the illustration is made from the diagrams as reproduced in Prof. Frey-Wyssling's

* Substance of a lecture in a series, "Case Histories in Biological Discovery", delivered during Trinity Term in the University of Oxford, and arranged by Dr. A. C. Crombie and H. B. Havré.

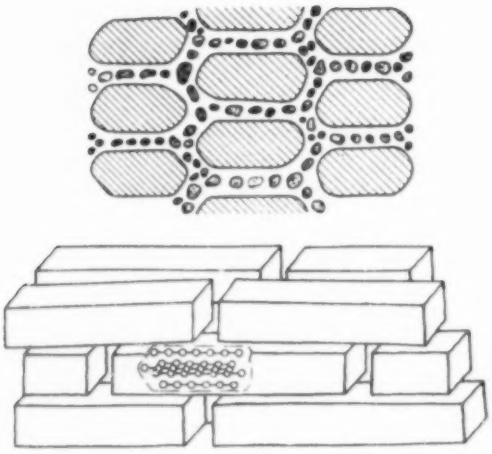

Fig. 1. Former conception of the micellar structure. Above, from Nägeli and Schwendener (1877); below, from Seifriz (1929) and K. H. Meyer (1930). (Above, reproduced by permission of Elsevier Publishing Co. from Frey-Wyssling, *Submicroscopic Morphology of Protoplasm*, Fig. 59; and below, by permission of *The American Naturalist*)

book, *Submicroscopic Morphology of Protoplasm*, of 1953, by kind permission of the author and of the Elsevier Publishing Co., of Amsterdam).

There is some superficial resemblance in the diagrams, but in fact the concepts represented are much nearer one another than are the diagrams: indeed, the concepts are virtually identical.

In the first place, Nägeli did not give a figure to illustrate his general notion, so we have to be content with one representing a particular case. Between the larger blocks, representing the micellæ, where in the general case there is simply water or some dilute aqueous solution, we see smaller blocks representing some incrusting material, such as lignin. To obtain a representation of the general case, we have to think these away; we then have only micellæ and water, as in Seifriz's diagram. Then, Seifriz has represented the constituent molecules of the micella, which should be shown in Nägeli's figure, but are not.

Seifriz's diagram[7] was drawn as an interpretation of results obtained in X-ray analysis by K. H. Meyer and H. Mark[8], and the diagram was accepted by Meyer as a correct interpretation[9]. Thus we find micellar order conceived in exactly the same way by Nägeli and by Seifriz and Meyer. Nägeli's figure was published in 1877; but the concept it illustrates was virtually perfected in 1858, and completely formed in 1863. This is sufficiently remarkable, even though

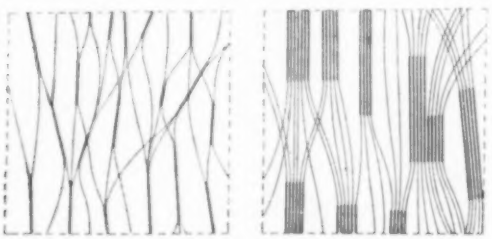

Fig. 2. Ordered regions in a gel framework. Left, locally parallelized chain molecules; right, local formation of a crystal lattice. (Reproduced by permission of Elsevier Publishing Co. from Frey-Wyssling, *Submicroscopic Morphology of Protoplasm*, Fig. 54)

more recent work has shown that the Seifriz diagram is a most inadequate representation of what seems to be the actual structure of cellulose. But this is not the end of the matter.

Nägeli's concept is, of course, intended to have a much wider generality than Seifriz's model, which was suggested only for the fine structure of natural cellulose; but Nägeli was, of course, as a botanist, particularly interested in the structure of cellulose, and his idea of micellar order was undoubtedly intended to explain, also, the structure of this substance as it occurs in plant cell-walls; so let us consider the further development of ideas on this structure.

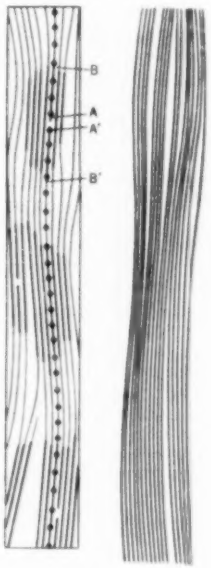


Fig. 3. Diagrammatic representation of the micellar structure of cellulose. Right, as suggested by K. H. Meyer. Left, micellar structure from primary valency chains (Kratky and Frey-Wyssling). The successive molecules, marked by circles, behave as a single molecule traversing the whole structure, since the ends, *A* and *A'*, lie within a crystalline region (thick lines). (Reproduced by permission of Interscience Publishers, Inc., of New York, from K. H. Meyer, *Natural and Synthetic High Polymers*, Figs. 87*a* and 87*b*)

Seifriz, in making his diagram, had neglected an argument already propounded by Sponsler and Dore in 1926[10]. Sponsler supposes that the polymer chains in plant-fibres must be of very great length, for one of the most striking features of plant-fibres is their very great tensile strength. This argument from tensile strength to continuity of polymer chain soon became widely known and generally accepted as valid. Thus later workers modified the Nägeli–Seifriz diagram (at least in its application to the fine structure of fibres) in various ways, to make it more consistent with the known facts of tensile strength of plant-fibres; though there were other reasons for modifying the original 'bricks in a wall' model, for it seemed that the length of the micellæ must be about 600 Å., the minimal length given by X-ray analysis, whereas Staudinger obtained values for the molecular weight of natural cellulose which would suggest a chain-length of 10,000 Å. It was suggested that one chain might belong to many micellæ. The model thus arrived at is illustrated in Fig. 2, also derived from a figure in Prof. Frey-Wyssling's book.

Although these drawings were prepared specially for the book published in 1953, they represent suggestions made earlier. On the left is a figure showing the fine structure proposed by Herrmann, Gerngross and Abitz[11] for gelatine, and on the right the new model for cellulose suggested by Prof. Frey-Wyssling[12].

It will be seen that this model satisfies both the requirement of micellæ (localized regions of crystal-order) and that of very long polymer chains. The chains lie parallel in some regions and are elsewhere arranged loosely. Where they are parallel they give a lattice with the optical properties of a crystal.

This notion of the fine structure of fibres was found unacceptable by K. H. Meyer[13], who suggested that the regions of lattice order were themselves continuous. "It seems more correct," he writes, "to represent the micellar structure as in Fig. 87*b* [on the right of Fig. 3 of this article], where no limit is set to the crystalline regions in the direction parallel to the fibre-axis."

The figure on the left shows a slight modification of the Frey-Wyssling model, a modification suggested by Kratky in 1938[14]. Fig. 4 shows Meyer's 'micellar ropes' in cross-section. The diagonal strokes represent the position of the 'glucose rings' (in the cellulose molecule), the regular arrangement of which gives the crystal lattice. This notion of micellar ropes is accepted by Prof. R. D. Preston, in his elegant monograph, *The Molecular Architecture of the Plant Cell Wall*, of 1952. Fig. 5 shows an electron-micrograph of a layer of the cell-wall of the alga *Cladophora rupestris* showing just such ropes as Meyer had postulated. Prof. Preston has kindly supplied me with this micrograph.

We seem to have come a long way from Nägeli's model. In fact, however, this development of ideas took place in Nägeli's mind between 1877 and 1879, for in 1879[15] he himself suggested that the tensile strength of plant-fibres requires a modification of the model of 1877, and pointed out that what is required is that the micellæ should "grow together" end to end, so as to form continuous strands.

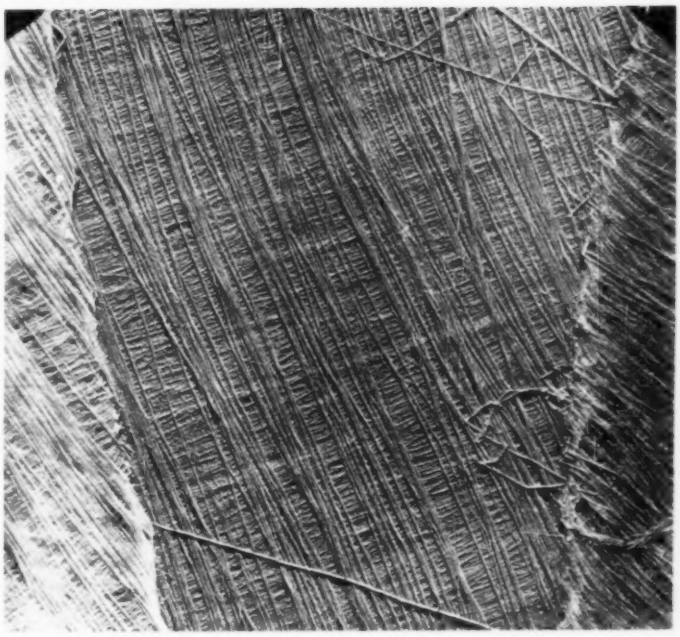

Fig. 5. Electron micrograph of inner-wall lamellæ of *Cladophora rupestris* viewed from outside. Palladium-gold shadowed. Top to bottom is direction of cell axis. (× 24,000.) (From V. Frei and R. D. Preston, *Proc. Roy. Soc.*, *B*, **154**, 70; 1961)

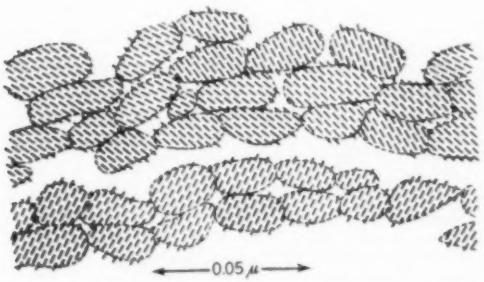


Fig. 4. Part of a schematic cross-section of two successive lamellæ of the cell-wall of a cellulose fibre. The strokes indicate the position of the glucose rings; the scale refers to the micellar ropes (the glucose rings are about four times too large). The micelles should therefore contain more glucose units. The spaces contain water, air or cementing materials. (Reproduced by permission of Interscience Publishers, Inc., of New York, from K. H. Meyer, *Natural and Synthetic High Polymers*, Fig. 90)

This must serve as an illustration of what I may call the 'predictive force' of Nägeli's ideas. It is clear that he must have obtained a true insight into the structure of the objects he was examining; for his predictions, if we may so call them, are too elaborate to be the results of mere luck. What then was his method? How did he arrive at these results?

It is often supposed that Nägeli's principal tool was the polarizing microscope; and if this had been the case it might perhaps be argued that the model of discrete crystallites surrounded by envelopes of water would be the simplest and most obvious for the observed phenomena. A starch-grain between crossed nicols shows the spherulite cross characteristic of a spherical body composed of radially arranged crystallites. Dry starch absorbs water, and in certain reagents starch-grains swell very greatly without losing their shape. Thus a system of radially placed crystallites with interspaces containing water seems, perhaps, an almost inescapable proximate hypothesis for the structure of the starch-grain. When it is added that cell-walls are also optically anisotropic and liable to swelling, the initial stage of generalization is also given.

The truth is, however, that Nägeli had completed his model for the fine structure of starch-grains before he made any extensive use of the polariscope. The model suggested in the monograph of 1858 is exactly that represented by the figure in my Fig. 1 (even the encrusting substance is here appropriate; for Nägeli knew that there are two substances in a starch-grain, though he incorrectly identified the less soluble as cellulose). Indeed, the figure (Fig. 1, here) is particularly apt to illustrate the concept of 1858,

for it shows no internal order in the micellæ of starch; and in 1858 he had not yet decided that the micellæ were micro-crystals[4]. He says explicitly that the forces holding the individual molecules (then called 'atoms') together within the micellæ are "analogous to the forces of crystallization", but are not identically the same as these forces; for starch is formed in the plant from aqueous solution, but is not itself soluble in water, which it would be (he argues) if composed of crystals.

This statement is of the first importance. In the first place it shows, I think conclusively, that Nägeli was not then using the polarizing microscope. Then, it seems to me that, had he from the first believed that the compound molecules, later called micellæ, were in fact crystallites, he might have had more difficulty in conceiving that idea which is, if not identical with the notion of polymerization, at the least a close precursor. For the molecules, or 'atoms of starch' as he then called them, would simply have been united by what seemed to be the familiar forces of crystallization, and no new and unexplained forces need be postulated.

I will now attempt to give some idea of the process by which Nägeli arrived at his most important hypotheses. As I have pointed out, most of these hypotheses are already formulated in the monograph on starch-grains, of 1858. This monograph is a huge work of more than 600 quarto pages, of which probably 550 are in a type usually reserved for footnotes. Though I have read it, it cannot be expected that I should do more here than give a summary account of what seem to me to be the most significant observations and the most important arguments.

The notion of a system composed of solid particles each surrounded by an envelope of water, a system which, however, is itself solid and rigid, was partly suggested by the phenomena of imbibition and of swelling, particularly swelling without loss of shape, but also, I think, by his belief that starch-grains grow by intussusception. From a review article by N. P. Badenhuizen[16], I gather that there is little doubt that starch-grains grow by deposition on the outer surface, and not by intussusception, so that this looks like an erroneous belief leading to a truth. But I think it likely that Nägeli had first formed the much more probable hypothesis[17] that cell-walls must grow at least partly by intussusception, and that this inclined him to believe that the same could be asserted of starch-grains. He does refer in his monograph to the immense growth in length of some cylindrical cells, and argues cogently that this can scarcely be accounted for by passive stretching of an already formed wall[4]. Naturally the space allotted to the consideration of cell-walls cannot be very great in a monograph on starch-grains, and it is possible that they were of greater importance in Nägeli's theorizing than the space assigned to them would suggest.

The hypothesis of supermolecules (polymers) is of great interest, and I am far from certain that all the influences leading to it are made explicit in the monograph. I suspect that this idea was latent in the earlier work on osmotic phenomena, which was certainly well known to Nägeli, as it was to Graham (the first volume of the *Pflanzenphysiologische Untersuchungen*, dated 1855 and published with the second volume, *Die Stärkekörner*, dated 1858, is concerned exclusively with osmotic phenomena); but this is a subject which I have not yet been able to investigate.

The explicit argument seems to be:

(1) Starch-grains are composed of alternating layers of dense and loose material, the loose material being much richer in water than the dense.

(2) The whole grain is, however, certainly all starch (or at least, the cellulose which he thought to be present is evenly diffused throughout the grain, and does not account for the difference between the layers).

(3) The only explanation of the difference in water-content in the alternate layers is that the particles of starch are larger in the dense than in the loose layers; but, since both large and small particles are chemically starch, the larger must be compounded from the smaller, which, of course, cannot be less than one molecule each.

(4) Nägeli also asserts that the larger particles cannot be isodiametric, but must be elongated in the direction of the radii of the starch-grain. This is, of course, a subsidiary proposition, and the hypothesis of compound molecules does not depend on it; but it is of considerable importance in the development of the theory of fine structure.

All these conclusions, which together give an outline of the main argument, seem rather poorly supported when examined individually. Nägeli could not be very certain that the layers differed only physically, not chemically, from one another; though he gives evidence for his belief that the difference could not be due to the second substance which he thought to be cellulose: if the starch is digested out with ptyalin, a complete ghost of 'cellulose' remains.

The conclusion that the difference is physical would receive powerful support from Nägeli's mathematically developed argument based on the supposition that growth is by intussusception; but the basic supposition is erroneous.

Nägeli's arguments[4] for the existence of larger compound molecules in the dense layers of the starch grain are extremely complicated, and it is not easy to decide the degree of interdependence between the parts of the whole logical complex.

Two main arguments seem to be involved:

First there is an elaborate dynamical argument, based on the supposition that organized materials have the kind of structure illustrated in Fig. 1—a sort of 'bricks in a wall' structure. The model is itself suggested by the belief that there are only two possible fine structures: the 'bricks in a wall' on one hand, and a network structure on the other. The network-model is then eliminated by the following argument. Starch can swell to 27 times its original volume; it then contains 90–98 per cent water, and between 10 and 2 per cent starch. Some cell-walls may probably contain as much as 200 or more parts of water to one of solid. If the solid parts formed a kind of scaffolding full of holes able to contain water, it would follow that starch and cellulose must possess a high degree of extensibility, a property entirely foreign to them. Further, it would necessarily be possible to express water by mechanical means but this is not possible with the cellulose-jelly. He notes that extremely aqueous cellulose walls may even be brittle.

To account for both rigidity and swelling of the system, he postulates two forces, one attracting starch to starch, and the other attracting starch to water. He supposes the starch–starch force to be inversely proportional to some power of distance, and the starch–water force to be inversely proportional to some higher power of distance.

Thus, $F_{ss} = \frac{A}{D^p}$ and $F_{sw} = \frac{B}{D^{p \cdot q}}$

where $p$ and $q$ are positive, and $A$ and $B$ are parameters.

At some distance determined by the parameters, which of course are constants for any one system, the forces will be equal. At any lesser distance than the distance of equality, the starch attracts water preponderantly; at any greater distance, starch attracts, preponderantly, starch. This gives us the repetitive pattern of blocks of starch separated by layers of water and allows for forced drying and re-imbibition with water.

An extremely elaborate development of this fundamental dynamic idea enables him to show that, given the initial postulates, the width of the layer of water would be greater if the particles of starch were smaller. Thus, if his mathematics and dynamics are correct, the postulates deliver a hypothesis connecting particle size with quantity of water. So, accepting that all particles are chemically starch, the notion that the compound molecules in the dense layers are larger than those in the loose layers acquires a certain status. That status remains, however, rather tenuously hypothetical. That he really came to believe in compound particles in this way is improbable, and he gives at least two much more direct arguments.

"Now it is possible to conceive of the relation of the particles of solid starch to the enveloping water in two ways: either that each atom of starch (consisting of 12 atoms of carbon, 10 of hydrogen and 10 of oxygen) is surrounded by an envelope of water, or that several atoms of starch are united to form a molecule, lying in an atmosphere of water . . . the fact that the water-content of solid starch varies between widely separated limits cannot be reconciled with the supposition that each atom of starch is surrounded by an envelope of water; for then . . . they would have to have a variety of properties . . . in the solid state; they would have to attract water in various quantities. In a word, there would have to be as many modifications of insoluble starch as there are different amounts of contained water. We are therefore led to adopt the second supposition as the more probable"[4]—that is, the supposition that different numbers of starch-atoms can combine to form starch-molecules of different sizes. When, in the passage just quoted, Nägeli speaks of starch containing very different quantities of water, he is thinking of the swelling of starch-grains on treatment with heat or with reagents. He must therefore argue that treatment of starch with the reagents concerned does not alter the starch chemically, and he writes:

"It is not possible to explain this phenomenon merely by the supposition that starch possesses for acids, for alkalis and for water at higher temperatures a greater affinity than for water at lower temperatures. Were this the cause of swelling, it would follow that, on the neutralization of the acids or alkalis and on cooling, the fluid taken up in excess must be released[4]."

He also notes that in all these cases, the swelling is a threshold phenomenon; heating must reach a certain temperature, and acids and alkalis a certain concentration before there is any swelling at all. The degree of polymerization he postulates can be judged by his computing the possible number of starch-atoms in a molecule to be "up to 9,000".

We may now consider how he attempts to prove that the compound (or polymer) molecules must be elongated in general form.

He argues that the rigidity of the whole structure (starch-grain or cell-wall) requires that the solid particles exercise different attractions in different directions, and he considers that it is "simpler and more natural" to suppose that this is due to their being anisodiametric, rather than to postulate different forces exercised in different directions by isodiametric particles[4].

This argument, which was probably correct in 1858, prevents him, I believe, from completing a most ingenious and characteristic argument based on the phenomena of cracking of starch-grains in shrinking or in swelling. From the space given to these phenomena in the more empirical part of his monograph, and from their being explicitly referred to in the theoretical part, it seems that they impressed his mind strongly.

Starch-grains are commonly composed of concentric spherical or ovoid shells, but when they are dried they do not, he says, show fissures between the shells, but very often do show radial cracking. This he interprets as proving that the particles "must have a radial as well as a concentric ordering". I cannot find that he anywhere makes clear that a mere geometrical ordering of particles in rank and file scarcely explains the observed phenomena. Unless I am greatly mistaken, what is required is a difference of attraction between particles; the attraction being greater along the radius of the starch-grain than in the tangential direction. If this could be conceded, we at once arrive at rod-shaped compound molecules with their length along the radius of the grain. But this would, of course, not be consistent with the postulate that isodiametric particles, such as he supposed the starch-atoms to be, must not be required to exercise different attractions in different directions.

Yet, in this discussion of cracking, which occurs early in the monograph, he does seem to have made up his mind on the presence of rod-shaped compound molecules; for, noticing that cracks occur also in the radial direction when the grain swells under reagents, he adopts as an explanation that in this case water-particles are inserted preferentially along the radius, which increases the radial dimensions relatively, just as in drying the radial dimensions are relatively increased by the removal of water lying principally tangentially between particles. Neither of these explanations seems to be very lucid unless we do assume that different forces are operative between the starch particles in the two directions, radial and tangential respectively.

Compared with the mass of work under review, my account, long as it is, is inadequately brief. But if it is of any value at all, what conclusions does it seem to hint at? Some conclusion I feel called on to offer; for a case-history without a diagnosis is necessarily disappointing.

It seems to me probable that the elaborate theorizing in which Nägeli indulged was to a minor extent responsible for his conclusions: that its chief function was to fortify his mind; to give him courage to make his way through an immensity of tedious detail (he weakened his sight seriously by the extreme assiduity of his microscopic studies), and courage to enunciate with conviction conclusions partly, if not wholly, arrived at by a process of independent judgment exercised immediately on his observations. It is

not without significance that both Hofmeister and Pfeffer praise him for his *Scharfsinn*; which seems to be the same quality as that referred to by Aristotle under the name ἀγχίνοια, and called by Kant, *Mutterwitz*. This is something the lack of which, as Kant remarks, no schooling can make good. We cannot analyse it, but one of its characteristics appears to be the ability to judge the relative importance of a piece of evidence; this is illustrated, to give only one example, by Nägeli's willingness to alter his model, which seemed to fit a number of the facts, when he found it inadequate to account for the tensile strength of plant fibres. It does appear to be a faculty which many, but not all, great scientists have had in an unusual degree. Mendel must have had it supremely or he would have been as unable as were his contemporaries to digest the mass of facts offered by Gärtner. Claude Bernard, on the other hand, is perhaps an example of a scientist who lacked this power. His results seem largely the product of an excellent method, and when called on to guess he commonly guessed wrong. Perhaps Faraday and Clerk Maxwell present a similarly contrasting pair.

The art of investigation, it may be, has, like other arts, its rules, by following which more can be accomplished than by the rules of other arts; but it has also, like them, an element which cannot be taught because it cannot be analysed.


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# THE RADIO TELESCOPE INTERFEROMETER AT THE ROYAL RADAR ESTABLISHMENT

By Dr. J. S. HEY, M.B.E.

A NEW installation for radio astronomical and upper atmosphere research at the Royal Radar Establishment, Ministry of Aviation, has recently been constructed on the site of a former airfield at Defford, near Malvern. The equipment consists essentially of two steerable and mobile radio telescopes with parabolic reflectors 25 m. (82 ft.) in diameter, which can be used either separately or in conjunction as an interferometer (Fig. 1.) The radio telescopes can be operated over a wide range of wave-lengths down to a few centimetres, and their spacing can be varied up to about 1,000 m. in any orientation for interferometric observations of high angular resolution. It is planned to use the aerials both as radiometers for the reception of radio emissions and also with transmitters for radar astronomy. The aim was to devise a radio telescope system which would combine sensitivity, accuracy and versatility.

Before describing the equipment in more detail some of the guiding principles governing the choice of system will be outlined. A parabolic reflector is particularly suitable for a radio telescope which is to be steerable in any direction and capable of changing wave-length easily. The sensitivity of a radio telescope when receiving radio emissions is proportional to its collecting area $A$; the least angle that can be resolved is approximately $\lambda/D$ where $D$ is the diameter of the aperture; when used with a transmitter in radio reflexion experiments the echoed signals are proportional to $A^2/\lambda^2$. The shortest wave-length to be used determines the accuracy required in the surface contour of the reflector, and surface deviations should not exceed $\lambda/16$ in working conditions (about 6 mm. at $\lambda = 10$ cm.). While metre wave-lengths are appropriate for much radio astronomical work there is an important field of research at shorter wave-lengths; consequently, it was planned that the system should be able to operate at wave-lengths as short as 10 cm. Unfortunately, constructional problems and cost increase rapidly with size of reflector when high accuracy has to be maintained. A reflector diameter of 25 m. was therefore accepted, and it was decided to use two radio telescopes as an interferometer in order to increase angular resolution.

When two separated aerials are connected together as an interferometer the aerial pattern consists of interference lobes with maxima separated at intervals of approximately $\lambda/L$ where $L$ is the spacing between the two aerials. The half-power width of each lobe is approximately $\lambda/2L$, compared with $\lambda/D$ for the half-power beam-width of a single aerial of diameter $D$. The angular resolution is thus greatly increased and is determined by the spacing; consequently, very accurate measurements of angular positions are possible on isolated sources. An interferometer with mobile aerials can be used for the determination of source diameters and the analysis of complex distributions of sources of radio emissions. This is achieved by the method of aperture synthesis in which observations obtained with the aerials at various spacings in different directions are combined. The resolution corresponds to that which would be achieved by exploring the sources with the very narrow beam produced by an aperture of dimensions comparable with the largest spacing.

The pointing errors of the radio telescopes must clearly be small compared with the beam-width. A 25-m. reflector gives a beam-width of about 20 minutes of arc at $\lambda = 10$ cm., so the pointing errors should not exceed 2–3 minutes of arc. The accuracy of the interferometer depends on the length and stability of the base-line. A variable spacing up

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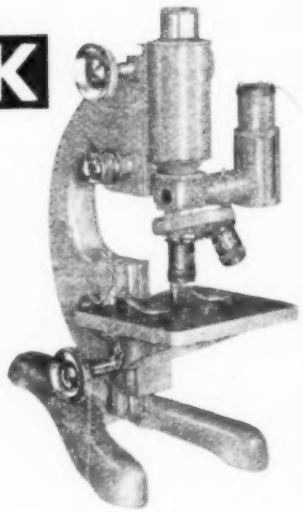

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to about 1,000 m. was chosen as appropriate for many purposes in the wave-length range of 10 cm.–1 m. To ensure an angular accuracy of a few seconds of arc it was specified that when operating at a given spacing the distance between the phase centres of two aerials should not vary more than 1 cm. and relative displacements at right angles to the line joining them be not more than a few mm.

The main contract for the equipment was placed with Werkspoor, which possessed unique qualifications in having previously constructed in Holland an accurate radio telescope of the required size as well as having special experience in the design and manufacture of traction equipment, bridges and large-scale structures. Several sub-contracts were arranged with British firms, and in particular the radio telescopes were erected at Defford by Carter-Horseley (Engineers), Ltd.

Several factors determined the choice of a site: it had to be nearly flat over distances of about 1 km. and with no screening of the field of view above a few degrees elevation, with freedom from sources of radio interference, and within a reasonable distance of the main Establishment at Malvern. The former Defford airfield fitted these requirements satisfactorily as well as providing runways suitable for the laying of tracks to support the mobile aerials, which are steel constructions each weighing about 240 tons. Two intersecting runways were required and the disposition of the tracks is shown in Figs. 1 and 2. The length of the tracks from the intersection is about 750 m. One aerial can run along the track in direction *AB* and the other along *CD*. It will be seen that any relative position can be achieved, the maximum spacing being 700–1,200 m. depending on direction. Along each runway are two parallel sets of standard double railway tracks 90 ft. apart. Each radio telescope is supported on a triangular carriage which can be electrically driven along the tracks. When they have been brought to the required positions for an experiment, the radio telescopes are levelled by means of hydraulic jacks. On each aerial, running, braking, levelling and locking are all controlled from one panel.

Although the radio telescope reflector is closely parabolic in contour, it is in fact polyhedral and consists of 1,464 triangular facets. These are in sets of 4, each set being separately adjusted to the correct position after mounting in the reflector framework. In this way a high accuracy of contour, within the specified limits for 10 cm. wave-length, can be attained. The reflector is constructed of wire mesh to minimize differential heating and consequent distortion, and also to reduce heat reflected to the focus during solar observations. The central region, of 20-m. mean diameter, is of fine mesh composed of wires 1·25 mm. in diameter with 7·25 mm spacing. The remaining outer part, to 25 m. diameter, is of slightly thicker wires with about twice the spacing. This concession in the

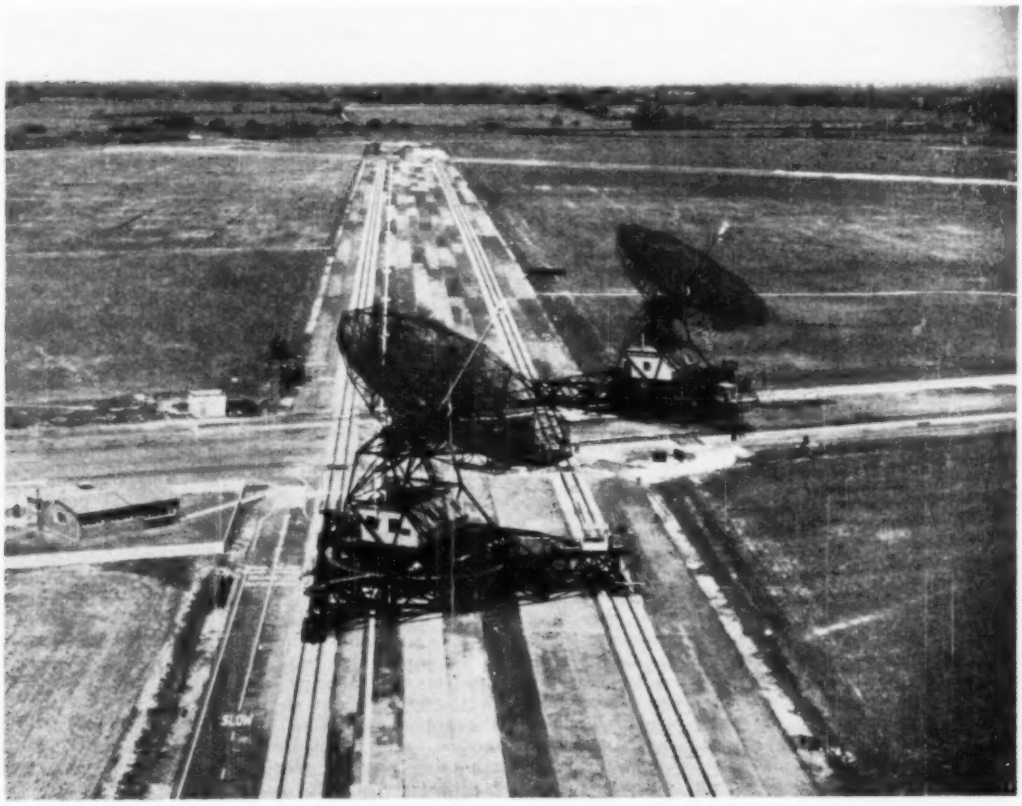


Fig. 1. The radiotelescope interferometer (Crown copyright)

outer mesh eases mechanical construction without serious detriment to performance, since it entails only a small loss of reflexion efficiency at 10-cm. wave-length. In any event, when highly sensitive radiometers are operated at short wavelengths, it is sometimes advisable not to attempt to utilize the whole reflector since 'spill-over' tends to bring in unwanted radiation from the ground. The focal length of the reflector is approximately 12 m., and the position and polarization of the aerial feed at the focus are adjustable during operation by a mechanism behind the reflector.

The reflectors have alt-azimuth mounts, and are provided with servo-motor drives. The central pivot for azimuth rotation takes about half the load, the other half being shared by four wheels running on a horizontal circular rail of 16 m. diameter mounted on the mobile carriage. The system is designed to give a pointing accuracy of better than 3 min. of arc at azimuth and elevation-rates up to 18° and 12° per min. respectively in normal working conditions and wind speeds up to 20 m.p.h.

Each aerial is provided with a mechanical analogue converter or 'pilot' which automatically transforms celestial co-ordinates of declination and hour angle into azimuth and elevation. With this device a celestial object such as a radio star can be followed continuously. When the two radio telescopes are used together as an interferometer they must track simultaneously in the same direction, and they must be connected together to combine the radio signals they receive. The first requirement is met by providing a control room at the intersection of the runways where the directional data of the radio telescopes are displayed and from which both equipments can be controlled. In meeting the second requirement the interconnecting cables must satisfy certain stringent conditions: there must be little change of electrical length due to temperature fluctuations or moisture, and reflexions at connecting points and attenuation in the cables must be small. Coaxial cables are used of which the outer conductor is a solid aluminium tube filled with dry pressurized air, and the inner conductor is held by a helical membrane spacer. For thermal insulation and protection, the cables are surrounded by glass wool and bituminous felt and placed in concrete cable ducts. Connecting boxes are placed at intervals of about 50 m. along the cable run as indicated in Fig. 2. The connectors are specially designed to minimize discontinuities and consequent reflexions.

The cabins mounted behind the aerials are each large enough to accommodate two high-power radar transmitters as well as receiving and other apparatus. If desired, one aerial may be used for transmission and the other for reception to eliminate some of the difficulties which can arise in common transmitter-receiver systems with highly sensitive receiving devices. At present, a transmitter with 2½ MW. peak-power and 5 μs. pulse-length working at a frequency near 1,300 Mc./s. has been installed in one of the cabins, and in the other a transmitter with 100 kW. peak-power, 200 μs. pulse-length, with operating frequencies at 300 Mc./s and 500 Mc./s. At 3,000 Mc./s. it is planned to utilize the 2 MW., 5 μs. transmitter already available in the 45-ft. radio telescope at Malvern.

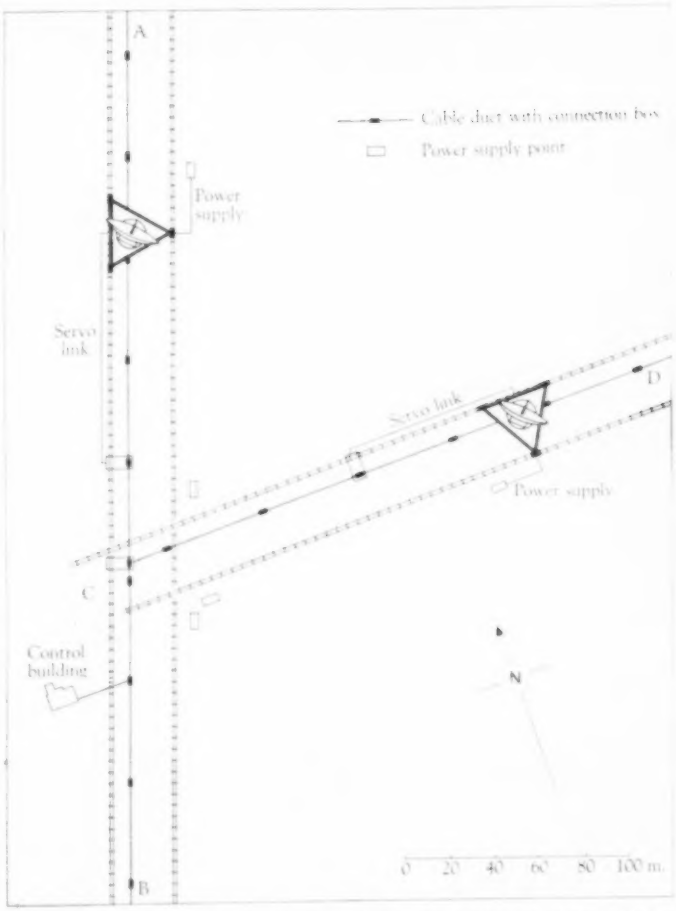


Fig. 2. Diagram of central part of the installation. The total length of the track in direction *AB* is 1,500 m. and that in direction *CD* is 750 m.

It will be appreciated from this description that the new installation is a major addition to British facilities for the radio exploration of space. It is a suitable instrument for observations of radio emissions originating from many different sources such as radio stars, the Sun, Moon and planets, Earth satellites and space probes. Within the solar system radar methods can also be applied. In the upper atmosphere, investigations can be made of meteors, auroræ, and ionospheric phenomena. The radio telescope system combines versatility and high angular accuracy for a wide variety of research in radio astronomy and the radio phenomena of the upper atmosphere.

# NEWS and VIEWS

## The Henry Dale Professorship of the Royal Society

THE Council of the Royal Society has accepted a generous gift of £100,000 from the Trustees of the late Sir Henry Wellcome to establish and endow a Royal Society professorship in medical research to be known as the Henry Dale professorship. The Wellcome Trustees have made this gift to commemorate the unique services of Sir Henry Dale to the Trust as its chairman for twenty-two years as well as his outstanding contributions to science and medicine in a wider context. In accepting the gift, the Society expresses its gratitude and great satisfaction in being associated with the Trustees in this act of honouring its distinguished Fellow, Sir Henry Dale, who has also rendered conspicuous service to the Society both as secretary (1925–35) and as president (1940–45). The Council of the Royal Society greatly values this outstanding benefaction, which will significantly increase the Society's capacity to promote medical research. The appointments to the new professorship will be especially, but not necessarily exclusively, in relation to research in physiology and pharmacology, which are the particular interests of Sir Henry Dale. This announcement of the establishment of the new professorship was made on Sir Henry Dale's eighty-sixth birthday, June 9.

## The National Institute for Medical Research: Sir Christopher Andrewes, F.R.S.

SIR CHRISTOPHER ANDREWES retired on June 6, after thirty-four years service as a member of the scientific staff of the Medical Research Council: he was head of the Division of Bacteriology and Virus Research at the National Institute for Medical Research, and had been deputy director of the Institute since 1953. Sir Christopher's scientific career coincides closely with the modern development of medical virology, and he is recognized internationally as an authority in this field. His name will always be associated with the outstanding work that led to the discovery of the influenza virus; in this he played a leading part, and the viruses of influenza and other respiratory diseases have remained his principal scientific interest. This is illustrated by the courageous decision that was taken by the Medical Research Council, on the personal initiative of Sir Christopher, to set up a research group under his direction in the Harvard Hospital at Salisbury for the long-term study of the elusive problem of the common cold. The combined laboratory and human volunteer organization that he established was universally recognized as being admirably designed for this type of work, and it is most gratifying that Sir Christopher's persistence in the face of repeated disappointments should have been rewarded by the discovery at Salisbury, a year before his retirement, of methods of isolating and cultivating common cold viruses. Sir Christopher has also contributed to the increasingly important subject of the nomenclature and classification of viruses. He has lectured on his subject in many countries and he has trained many pupils; the present flourishing state of medical virology owes much to his work and influence.

## Dr. A. Isaacs

SIR CHRISTOPHER ANDREWES is succeeded as head of the Division of Bacteriology and Virus Research at the National Institute for Medical Research by Dr. Alick Isaacs. Dr. Isaacs qualified in medicine at the University of Glasgow in 1944. After house appointments and the tenure of a research scholarship in the Department of Bacteriology in Glasgow he spent a year in the Department of Medicine at Sheffield, and then worked for two years with Sir Macfarlane Burnet in Melbourne; this experience has had great influence on his subsequent career. Dr. Isaacs joined the scientific staff of the Medical Research Council in 1950 in order to work at the National Institute for Medical Research in the Division of which he is now taking charge, and during the past ten years he has established himself as a leading research worker in virology. His interests have lain chiefly in influenza and related viruses, and he has been responsible for the World Influenza Centre which was set up at Mill Hill, in co-operation with the World Health Organization, for the study of the epidemiological aspects of the disease, particularly in relation to the appearance of new strains of virus and their influence on the spread of epidemics from country to country. During the past few years Dr. Isaacs' work has attracted much attention through his discovery of interferon, a substance produced in cells as a result of viral infection, which has an inhibiting effect on viral growth. This is a discovery with widespread implications, and it has aroused interest and stimulated new research in laboratories throughout the world.

## Mineral Technology at the Imperial College of Science and Technology: Prof. M. G. Fleming

DR. M. G. FLEMING, who has been appointed to the new chair in mineral technology in the Department of Mining at the Imperial College of Science and Technology, is a graduate of Queen's University, Kingston, Ontario. On leaving college he spent four years in the mining industry, finally holding the appointment of chief metallurgist at the Paymaster Gold Mine, Ontario. Following the outbreak of the Second World War, Fleming joined the Royal Canadian Air Force, and after various appointments in Training Command flew as flight lieutenant navigator with 435 Squadron from Down Ampney, Gloucestershire. On his return to civilian life in 1946, Fleming was appointed to the staff of the Royal School of Mines, which is one of the constituent colleges of the Imperial College, becoming senior lecturer in 1951 and reader in 1958. These years since the War have seen the establishment of the new degree course in mineral technology following the opening of the Mineral Dressing Laboratories in 1953. Fleming's main research interest has been connected with investigations into flotation phenomena, particularly the characteristics of secondary lead minerals, and he has also given much attention to the application of basic research to plant operation. He is well known for his work in both these fields and has been consulted frequently by industry and

overseas Governments. As a consequence, he has travelled widely and has first-hand knowledge of mining conditions in many parts of the world, which, coupled with his research experience, will prove to be of particular value to the Royal School of Mines while building up the traditions of the new Department—a Department the work of which is devoted to one of those fascinating areas to be found lying between pure science on one hand and conventional engineering on the other, and which only now are beginning to be investigated systematically.

## The National Institute of Agricultural Botany : Dr. P. S. Wellington, D.S.C.

Dr. P. S. Wellington has been appointed assistant director of the National Institute of Agricultural Botany as from July 1, 1961. The vacancy was caused by the death of Mr. G. W. G. Briggs (*Nature*, 190, 861; 1961). Since 1952, Dr. Wellington has been the chief officer of the Official Seed Testing Station for England and Wales, which is one of the branches of the Institute. In this position he has been responsible for statutory tests under the Seeds Act and has initiated a programme of investigations into the problems arising from new methods of handling and conditioning the seed of farm and garden crops. Dr. Wellington is a graduate of the University of London, where he obtained first-class honours in botany at the Royal College of Science (Imperial College). During the War he served as an observer in the Fleet Air Arm and was awarded the D.S.C. in 1941.

## International Meteorological Organization Prize for 1961 : Prof. K. R. Ramanathan

Prof. K. R. Ramanathan, of the Physical Research Laboratory, Ahmedabad, has been awarded the International Meteorological Organization Prize for outstanding work in meteorology and international collaboration. Prof. Ramanathan studied at Victoria College, Palghat, and Presidency College, Madras, and after obtaining a doctor's degree in science, he became a demonstrator in physics at Trivandrum College and later a research scholar at the University of Madras. In 1922 he joined Rangoon University College as a lecturer in physics. In 1925 he became a member of the Indian Meteorological Department. After having been director of the Kodaikanal and Bombay Observatories, he was appointed deputy director-general of observatories. In 1948 he was appointed director of the Physical Research Laboratory in Ahmedabad. Prof. Ramanathan has worked on problems of molecular scattering of light in fluids, atmospheric and solar radiation, study of the Indian monsoon, general circulation of the atmosphere, atmospheric ozone, physics of the ionosphere and aeronomy. For several years he was the president of the International Union of Geodesy and Geophysics, and was also president of the International Association of Meteorology of that Union. He has been, and still is, the president of the International Ozone Commission. The International Meteorological Organization Prize was established in 1955 by the World Meteorological Organization in honour of the former non-Governmental organization which had initiated international collaboration in meteorology in 1878, but which ceased in 1951 when the World Meteorological Organization took over. The Prize consists of a gold medal and 1,200 U.S. dollars.

## Taxation of Scientific Bodies

On the second reading of the Rating and Valuation Bill in the House of Lords on May 31 the position of the scientific societies was strongly represented by the Earl of Halsbury, the Earl of Cranbrook and Lord Douglas of Barloch, though Earl Jellicoe had not mentioned this question in moving the second reading. Lord Hailsham, in replying on the debate, said that there is a prospect of fairly general agreement between the Government and the learned societies about the way in which the problem should be tackled (see *Nature*, May 20, p. 657). He referred again to the deputation he had received on behalf of the societies, but repeated that he did not think it would be right to deal with the question within the scope of the present Bill beyond the 50 per cent mandatory relief. It would not be right to ask local authorities to undertake what was fundamentally a national burden. Lord Hailsham said that he recognized to the full what Lord Halsbury and Lord Cranbrook had said about the value of the work of these societies, that many of them are essential to the working of science, that they produce publications and maintain libraries of national importance, but his own opinion was that the difficulty could not be dealt with by rate relief at all, but that it must be dealt with by grants in some form. He thought we should consider using the Royal Society and the British Academy as vehicles for this kind of negotiation, and if they were prepared to act the Government would be glad to hear from them as and when the situation developed.

## United Kingdom–Euratom Technical Collaboration

In a written answer in the House of Commons on June 6, the Parliamentary Secretary for Science, Mr. D. Freeth, said that co-operation under the United Kingdom–Euratom Technical Collaboration Agreement had covered a wide range of subjects. These included basic reactor physics, reactor planning and programming, reactor economics and the costing of nuclear power, fast reactors and gas-cooled reactors, thermonuclear fusion, nuclear measurements, mass spectrometry, workshop organization, health and safety, corrosion, the construction of 'hot' laboratories, the industrial applications of radioisotopes, juridical problems arising from nuclear ship propulsion, radiation protection and third-party liability. Co-operation had proceeded by exchange of reports, visits of experts, conferences and symposia, and attachment of staff to specific projects and establishments. The United Kingdom also collaborated with Euratom and the United States Atomic Energy Commission in the translation pool "Transatom", which concentrated on translations from Russian and Japanese.

## Funds for Cotton, Silk and Man-Made Fibres Research

The Cotton Industry Development Council (Amendment No. 4) Order, 1961, which was approved by the House of Commons on May 8, enables the Cotton Board to collect a statutory levy from firms processing man-made fibres, to support the British Cotton, Silk and Man-Made Fibres Research Association, which is being formed by the merging of the British Cotton Industry Research Association and the British Rayon Research Association, as recommended last year in the report of the working-party appointed by the Councils of the two Associations (see *Nature*,

190, 589; 1961). Article 6 of the Amended Order enables the Cotton Board to collect from the man-made fibres section of the industry 11 per cent of the total being collected from the whole industry, which in 1959–60 and 1960–61 was £385,000. For 1961–62 the total proposed to be collected from the industry for all the Cotton Board's activities was £400,000, of which £45,000 would come from the man-made fibres section, and, with £200,000 from the cotton section, would go to the Research Association. The Order also enables the Cotton Board to assist scientific research on the man-made fibres side. In reply to a question, Mr. N. Macpherson, Parliamentary Secretary to the Board of Trade, who moved the approval of the Order, said that one object of the merger was to reduce expenditure; the income of the Shirley Institute was £462,000 in 1959–60 and was expected to be £531,000 in the first year of the next quinquennium: that of the Rayon Research Association had been £376,000.

## The Devon Naturalists' Trust

THE Devon Naturalists' Trust was formally inaugurated on March 27. Its objects are to conserve the wild-life of the county against encroachment, to protect places of interest to naturalists, and to encourage the study of natural history. Lord Roborough is the first president. A public meeting to invite support was held in Exeter on May 16, and the speakers were Lord Roborough, Lord Hurcomb, Mr. H. G. Hurrell and Major J. Coleman-Cooke. Mr. Hurrell announced his gift to the Trust of Lady's Wood, its first reserve. This is an area of some 9 acres near South Brent which contains much of interest, including dormice and wood anemones. Apart from the reserve given by Mr. Hurrell, there is a strong possibility that the Trust will be offered another. It is also in contact with a farmer who has a large colony of *Lobelia urens* on his land, and it is hoped to do something to preserve this very rare plant. The Trust and the Devon Wild Fowlers Association are acting together to see if the management of the bird sanctuary on the River Exe can be improved. The prospects of introducing blackgame and *Zostera marina* in suitable places is being studied and may be put in hand if the initial inquiries indicate a good chance of success. The Trust is also making inquiries to discover if the commercial primrose picking reported in the Press last spring is likely to be damaging.

## Conservation of Askham Bog

THE Nature Conservancy and the Yorkshire Naturalists' Trust have agreed to conserve Askham Bog. This area, near York, is a 100-acre remnant of a swamp which must at one time have covered much of the Vale of York. Now almost wholly covered by a thicket of birch, oak and alder, the Bog illustrates the later stages in the succession from open fen to woodland. The ground vegetation includes many bog and fen species uncommon in Yorkshire, among them the rare royal fern. Associated with this flora is a rich variety of insects, particularly beetles. The land is partly owned and partly leased by the Yorkshire Naturalists' Trust, which manages it as a nature reserve. At present it is managed successfully with due regard to the scientific interest and, accordingly, the Nature Conservancy does not feel it necessary to acquire a direct interest in the Bog or to declare it as a National Nature Reserve. By the agreement, Askham Bog is designated a Site of Special Scientific Interest (*A*). The Bog will continue to be managed by the Yorkshire Naturalists' Trust, advice from the Nature Conservancy being available when necessary. Permits to visit the site or undertake research there must be obtained from the chairman of the Management Committee, Mr. C. J. Smith, 7 Malton Way, Clifton, York.

## Aerial Photographs in Geological Mapping

IN the construction of geological maps, increasing use has been made in recent years of photo-geology, and to-day even the most junior research student tends to regard aerial photographs as a pre-requisite to his field work. Notwithstanding an extensive periodical literature, however, comprehensive and up-to-date text-books on this subject have been generally unavailable, and geologists throughout the world will therefore be indebted to Dr. Richard G. Ray, of the United States Geological Survey, who has produced an excellent monograph, *Aerial Photographs in Geologic Interpretation and Mapping* (United States Department of the Interior: Geological Survey, Professional Paper No. 373. Pp. vi+230. Washington, D.C.: Government Printing Office, 1960. 2 dollars). This well-produced prestige publication, sold at a nominal price, lucidly describes the photo-geological techniques employed not only in routine geological work but also in the search for petroleum and ore deposits, in engineering geology, and in hydrological investigations; and it furnishes a readable account of the instrumentation utilized in these studies. The text is illustrated by 116 figures, principally stereoscopic-pair photographs chosen from the collections of Government departments in the United States.

## The Australian Museum, Sydney

THE *Australian Museum Magazine* (13, No. 9; March 15, 1951. 3*s*.) includes an account of new aboriginal exhibits which have recently been placed on display in the Museum. One of the most successful of the exhibits illustrates how the aborigines make and use stone implements. Each technical process is demonstrated by using actual implements in vast hands and the impression is given of a native standing behind the exhibit and poking his arms through holes in the wall. The section on "Dress and Ornament" appeals to all visitors, and models of the various types of wind-breaks and huts, together with a painting of a camp scene, are equally arresting. The exhibits have been especially designed to be attractive and interesting to the casual visitor, instructive to those wishing to learn about the aborigine, and of service in the Schools Department. Other articles in this interesting *Magazine* deal with the gem-stones of Australia, fossil insects, freak fishes and the use of radioactivity in entomology and insect-pest control.

## Site for Ulster Folk Museum

THE Trustees of the Ulster Folk Museum have announced the purchase of the Cultra Manor Estate in County Down for the purposes of a site for a permanent folk museum. It includes a manor house and 136 acres of delightfully situated land overlooking Belfast Lough and the Antrim coast. The estate is about six miles from the centre of Belfast and is in an area unlikely to suffer from suburban development. Initial work on the land will start in the summer, and as much material for the Museum

has been gathered together since the Folk Museum was established by Act of Parliament some two years ago, it is hoped that developments will be well advanced in the foreseeable future.

## University News :

### Belfast

THE following appointments have been announced: Dr. A. Dalgarno, to the chair of quantum mechanics in the Department of Applied Mathematics; Dr. E. A. Cheeseman, to the chair of medical statistics in the Department of Social and Preventive Medicine.

### Bristol

DR. R. G. CHAMBERS has been elected reader in physics, also Dr. D. Bohm (until he takes up his appointment to the chair of theoretical physics at Birkbeck College). A. R. Paterson has been appointed lecturer in applied mathematics.

### Hull

THE following appointments to senior lectureships have been announced: Dr. G. C. Bond (chemistry); Dr. A. Cunliffe (physics); Dr. H. W. Parsons (mathematics).

### London

THE Wolfson Foundation has made a grant of £200,000 to University College, London. The money will be used to develop the Galton Laboratory and the Department of Eugenics, Genetics and Biometry in a building north of Euston Road which has been leased to the College by the University Grants Committee. The chair of biometry, vacant since Prof. J. B. S. Haldane left the University, will be re-established in the new premises.

### Nottingham

DR. JAMES CROSSLAND, lecturer in the Department of Physiology, University of St. Andrews, has been appointed reader in pharmacology in the Department of Pharmacy as from next session.

### Sheffield

DR. A. M. MURRAY has been appointed lecturer in physics.

## The Night Sky in July

NEW moon occurs on July 12d. 19h. 12m. U.T. and full moon on July 27d. 19h. 51m. The following conjunctions with the Moon take place: July 8d. 20h., Venus 2° N.; July 9d. 11h., Aldebaran 0·4° S.; July 16d. 03h., Regulus 0·3° N.; July 17d. 02h., Mars 0·3° S.; July 27d. 07h., Saturn 3° S.; July 27d. 17h., Jupiter 3° S. In addition to these conjunctions with the Moon, Venus is in conjunction with Aldebaran on July 16d. 06h., Venus being 3° N., and Mercury with Pollux on July 31d. 19h., Mercury being 6° S. Mercury is a morning star, and is visible low in the east before sunrise during the later part of the month. Venus is a morning star, rising at 1h. 20m., 1h. 10m. and 1h. 05m. on July 1, 15 and 31, respectively. Its stellar magnitude on July 15 is − 3·7; the visible portion of the apparent disk increases from 0·555 to 0·683 during the month, and its distance from the Earth increases from 73 to 96 million miles. Mars is too close to the Sun for easy observation. Jupiter and Saturn are visible almost all night, rising at about sunset and setting at about sunrise. Jupiter has stellar magnitude − 2·3 and Saturn + 0·3 on July 15, and their distances from the Earth on that date are 380 and 840 million miles, respectively, when they are in Capricornus and Sagittarius. There is one occultation of a star brighter than magnitude 6 visible at Greenwich: July 9d. 11h. 13·0 m., α Tau. disappearance; July 9d. 12h. 24·4m., α Tau. reappearance. The Earth is at aphelion on July 5, its distance from the Sun being 94·6 million miles.

## Announcements

PROF. C. W. WARDLAW, professor of botany and director of the Laboratories and Experimental Grounds in the University of Manchester, has been elected an honorary foreign associate of the Royal Academy of Belgium (Section of Natural Sciences).

DR. G. D. H. BELL, director of the Plant Breeding Institute, Cambridge, has been elected a vice-president of the National Institute of Agricultural Botany and a vice-president member of the Council.

DR. I. M. LIFSCHITZ of the Academy of Sciences of the Ukrainian S.S.R., Kharkov, has been awarded the Simon Memorial Prize by the U.K. Committee of the Low Temperature Group of the Institute of Physics and the Physical Society, for his work on the structure of the Fermi surface in metals and his work on liquid helium. The Prize, a memorial to Sir Francis Simon, a pioneer for the Low Temperature School of the Clarendon Laboratory, Cambridge, consists of £250.

FROM July 3, the address of the Director of the Service and all branches of the headquarters administrative office of the Public Health Laboratory Service will be: 24 Park Crescent, London, W.1; Tel. No. Museum 2223.

THE opening of the new Creep Laboratories of the Electrical Research Association, Cleeve Road, Leatherhead, Surrey, will take place on July 7. Further information can be obtained from Leslie Jervis, press officer, Electrical Research Association, Cleeve Road, Leatherhead, Surrey.

A CONFERENCE on "Behavior Genetics" will be held at the Center for Advanced Study in the Behavioral Sciences during August 14–September 3. Further information can be obtained from Preston S. Cutler, Center for Advanced Study in the Behavioral Sciences, 202 Junipero Serra Boulevard, Stanford, California.

AN international conference on "Heat Transfer", presenting new developments in theory and practice, will be held at the University of Colorado during August 28–September 1. Further information can be obtained from Alan Brown, director, Bureau of Continuation Education, University of Colorado, Boulder, Colorado.

A MEETING of the Photobiology Group will be held at the University of Sheffield during July 7–8. The programme will include papers on metabolism in photosynthetic bacteria and some aspects of photochemistry. Further information can be obtained from the secretary of the Group, Dr. D. Vince, Horticultural Research Laboratories, Shinfield Grange, Shinfield, Berks.

THE United Nations conference on "New Sources of Energy" will be held in Italy during August 21–31. The programme has been divided into a number of sessions, including (*a*) geothermal energy; (*b*) wind power; (*c*) solar energy. Further information can be obtained from the United Nations Information Centre, 14–15 Stratford Place, London, W.1, or the Executive Secretary, United Nations Conference on New Sources of Energy, United Nations, New York.

# RECENT SCIENTIFIC INQUIRIES IN PARLIAMENT

AT question time in the House of Commons on May 16, the Parliamentary Secretary for Science, Mr. D. Freeth, was faced with no fewer than 39 questions relating to scientific matters, ranging from the performance of the reactors at Calder Hall and Chapel Cross, progress with production of nuclear reactors for research and teaching purposes, to arterial disease and fire hazards of domestic equipment.

In the course of his replies, Mr. Freeth said that rather more than three-quarters of Great Britain has been covered by the Geological Survey in the primary 6-in. survey. At the present rate of progress the primary 6-in. solid and drift survey would be completed in about 55 years; it is hoped to reduce this to 35–40 years. Nearly as much secondary survey as primary survey is being carried out, and work is now being done on the more difficult mountainous regions. The Survey has also prepared the tectonic map of the United Kingdom as part of a co-operative scheme for a tectonic map of Europe.

On research into coal utilization, Mr. Freeth said that besides the British Coal Utilization Research Association, the British Coke Research Association and the Coal Tar Research Association are primarily concerned with the utilization of coal. All three research associations are doing very valuable work and there is a great deal of co-operation between them and between the National Coal Board, the Central Electricity Generating Authority, the Gas Council and the appliance and equipment makers. The total income last year of the Coal Utilization Research Association was £450,000, of the Coke Research Association more than £150,000 and of the Coal Tar Research Association less than £113,000. There was the fullest possible co-ordination on the matter between the Minister for Science and the Minister of Power.

Mr. Freeth was also asked what research was being conducted into the better use of the mineral resources of Britain; he referred to the basic information supplied by the Geological Survey and Museum in its maps and memoirs. The Warren Spring Laboratory and the National Chemical Laboratory undertake research on processing ores and extracting metals, and various research associations, industrial firms and universities undertake research into the better use of minerals.

Asked as to the action taken to apply scientific development to the machine tool industry, Mr. Freeth said that besides the scientific development work of the Machine Tool Industry Research Association and the Production Engineering Research Association, research of direct value to such scientific development was carried out at the National Engineering Laboratory and the National Physical Laboratory. In addition, 12 grants totalling more than £170,000 have been made for research and development work in this field in the past two years to six universities and two colleges of technology in England and Wales. The Machine Tool Advisory Council is reviewing progress made in implementing the recommendations of the Mitchell Sub-Committee. Mr. Freeth also referred to a ten-fold increase in the accuracy of large modern gears over the past twenty years, to which research and development work at the National Physical Laboratory and the National Engineering Laboratory had contributed. Gears up to 16 ft. in diameter can now be made with an error of one-quarter of a thousandth of an inch from the true form and spacing of the teeth and the automatic error-correcting system developed recently by the National Engineering Laboratory have been applied to a gear-cutting machine.

While the Department of Scientific and Industrial Research has not sponsored any research into the use and operation of multi-purpose pipe-lines for the transport of both liquids and solids, it is itself carrying out research into the subject, and the Department is always willing to discuss with industry the part it could play in assisting research and developing techniques in every field.

In response to a specific request which had been made for a breakdown of the figure of £42·9 million for Government expenditure on civil research and development in 1958–59 given in the report of the Advisory Council on Scientific Policy, Mr. Freeth gave the following figures for the source of the funds concerned: defence departments, £2·9 million; civil departments, £34·7 million; private industry, £4·5 million; other organizations, £0·8 million.

# MAWSON INSTITUTE OF ANTARCTIC RESEARCH

ON April 15 the Prime Minister of Australia (the Rt. Hon. R. G. Menzies) inaugurated, within the University of Adelaide, the Mawson Institute of Antarctic Research. In his inaugural address Mr. Menzies referred to the great achievements of Sir Douglas Mawson in science and exploration, and affirmed that Mawson had accomplished so much because he possessed, in the highest degree, the qualities of imagination, courage and endurance.

The University of Adelaide has established the Institute, believing that it would provide the best means to commemorate one of its most distinguished members. Mawson joined the University staff in 1905 as lecturer in mineralogy and petrology. In 1921, he was appointed professor of geology and mineralogy, and he retired in 1952. He remained a member of the University Council until his death in 1958.

The main purpose of the Institute will be to foster polar studies and research. In order to do this it will maintain and develop reference collections of geological and biological materials from the Antarctic.

It will maintain and develop a library of papers and maps as well as books on Antarctica. It will provide accommodation for workers engaged in antarctic research. It will promote public interest in polar matters by means of lectures and a museum devoted to antarctic materials and equipment.

The University plans to accommodate the Institute in a major annex to the geology school. This would contain a library in which the map collection would be included, a museum which would serve as a meeting-room, generous storage space and a number of small research rooms.

The basis of the reference collections will naturally be the materials collected by Mawson and members of the expeditions which he led, although valuable collections from other parts of Antarctica have been obtained by exchange with the British Museum and other institutions. At present these are largely housed in the Geology Department of the University. Many periodicals and other books have been segregated in a 'polar' room in the University library, and their number will soon be greatly increased as Lady Mawson has announced that she will present to the Institute the extraordinarily fine library collected by Sir Douglas.

To mark the inauguration of the Institute a small 'Antarctic Room' has been partitioned from the geological museum. This is mainly occupied by rocks arranged on a regional basis and well documented with maps and geological sections. It also serves to illustrate the achievements of the expeditions of which Mawson was a member or which he led.

The interest created by the inauguration of the Institute has been very wide. Representatives of the Royal Society and the Academy of Science of the U.S.S.R. were present and the Australian Academy of Science was represented by its president. Other institutions which were represented included the Royal Geographical Society, the American Geographical Society, the Argentina Institute of Antarctic Affairs and the Scott Polar Research Institute. Messages of goodwill and congratulations were read. In addition, the Governments of the United Kingdom and New Zealand sent representatives and, from the South Australian Government, two Ministers of the Crown attended. Many men with personal experience of antarctic exploration and research were present. The occasion revealed wide approval of the University's move and paid high tribute to a very great Australian. A. R. ALDERMAN

## TRAINING IN OCCUPATIONAL HYGIENE

THE twelfth Conference of the British Occupational Hygiene Society was held in London on April 11. The morning session, with Dr. J. C. Gilson in the chair, dealt with the need for training, and the afternoon, with Dr. L. G. Norman as chairman, covered present and future facilities in universities.

Dr. Gilson opened the proceedings by contrasting the considerable effort now being put into radiation monitoring with the meagre resources available for checking dust and fumes, which he estimated to be a risk to some 150 times as many people as were exposed to nuclear hazards. The disparity of effort on the job was reflected in training resources, and no university course in occupational hygiene existed.

The interest of management in working conditions was emphasized by Mr. H. F. Spencer, managing director of Richard Thomas and Baldwins, Ltd., who criticized the term 'occupational hygienist'. Dr. J. M. Rogan, of the National Coal Board, who directs one of the largest epidemiological investigations at present being made in the world, considered that the existing employment of industrial medical officers in large concerns, with specialist laboratory help when required, might be more satisfactory than the appointment of broadly trained occupational hygienists.

Dr. K. P. Whitehead of Imperial Chemical Industries, Ltd., and Dr. P. G. Swann of Esso gave accounts of the ranges of activity of the personnel whose health, as industrial medical officers, they had to safeguard. The former emphasized the diversity of the chemicals handled. In his firm an industrial hygiene research laboratory studied toxicity and advised on works policy and plant design. He could see little need for the employment of industrial hygienists at factory-level in large, well-organized industries although they might be of considerable benefit to smaller firms.

Dr. Capel's firm employed an industrial hygienist, a graduate in chemistry, who had been trained in the United States. His reports were countersigned by one of the medical staff. It was advantageous for the candidate for such a post to have a degree related to the activities of the firm, or possibly a degree in general science, in which case a six months' course in the principles and practice of industrial hygiene would be sufficient. The parent American company maintained a medical research division which served affiliates all over the world and provided toxicological data on all materials handled.

Mr. H. Collinson, chairman of the Trades Union Congress Social Insurance and Industrial Welfare Committee, concentrated on the problem of the small employer with a back-street factory where conditions were often appalling, although work in the highest tradition of craftsmanship might emanate from it. To some extent this was a matter of educating the employer who was unaware and uncooperative towards suggestions for improving working conditions, but it was unlikely that voluntary action was going to be sufficient. The responsibility for making occupational hygiene available to the whole range of industry rested on the Government. The T.U.C. attached great importance to the pioneer work being done by group health services, such as that at Slough. The Nuffield Foundation had recently placed a quarter of a million pounds at the disposal of the Ministry of Labour for the encouragement of such schemes.

It was important that training should include practical experience in factories, which could only be achieved by the persuasive powers of those planning courses.

Ten years experience in providing an occupational hygiene service for the 200 member firms of the Slough Industrial Health Service was described by Dr. D. Hickish. The firms ranged in size from 2 to 2,000 employees and the backing of the group medical

service was available. Recently, consultant work outside the group has been undertaken. The function of the occupational hygienist was : (*a*) to recognize environmental stress affecting health ; (*b*) to evaluate the stress ; (*c*) to prescribe control measures.

The occupational hygienist needed to have studied elementary physiology, industrial medicine and toxicology. Training in sampling and analysis, including dust, radiation and noise, detailed knowledge of heating, ventilating, air-conditioning and lighting, and a familiarity with statistical methods were desirable. Courses at a technical level, in addition to those for graduates, would be advantageous.

The deputy chief inspector of factories, Miss K. Crundwell, described a recent attempt to catalogue the facilities which at present exist for testing factory air. It was going to be difficult to convince industry of the need for testing to such an extent that they were willing to pay for it. Some employers were anxious to improve their working conditions but others might not take kindly to the suggestion that they should pay, as they might see it, for the evidence on which to hang themselves.

The last speaker in the morning session was Dr. S. G. Fortuin, director of the Philips Medical Services, Eindhoven, Holland. He explained that in every plant they tried to have a full-time medical man, whose services might also be shared by smaller firms in the same town. The checking of environmental conditions was the task of the medical department and there was no place for a more or less independent industrial hygiene department. The physician alone should be responsible for the evaluation of health hazards.

The industrial hygiene laboratory was part of the Medical Service ; chemists and engineers were employed in this work and no university programme existed in the Netherlands for training them in the specific theoretical and practical problems of industrial hygiene ; postgraduate courses should be organized for this purpose.

In the discussion which followed the first session it was generally agreed that a need for testing facilities existed, and this involved the training of occupational hygienists to carry out environmental measurements. The cost and method of paying for such services was debated and it seemed unlikely that small firms would be willing, or even able, to carry this individually, although trade associations might offer a way round the difficulty. Another problem was the cost of remedial measures, involving re-design of plant or exhaust equipment, which might be crippling to a small undertaking.

The afternoon session was opened by Dr. L. G. Norman. In a survey of courses related to occupational hygiene which are at present available, Dr. C. H. Wood said that very little was offered in Britain. British employers of occupational hygienists, when questioned, were unanimous in stating that the only training provided was in-service, augmented, occasionally, by short courses given, as a rule, by senior members of the staff.

It was difficult to find out what British teaching institutions gave in the way of special courses, as distinct from the comprehensive type in the United States, since no general list was published ; nevertheless quite a number of subjects could be investigated in this way, lectures on radiation hazards being liberally provided.

Mr. S. A. Roach gave an account of a nine-month course in industrial hygiene engineering which was being planned at the London School of Hygiene and Tropical Medicine and which was to open in October 1961.

Prof. R. E. Lane, who is responsible for the teaching of occupational hygiene in the University of Manchester, stated that the current course for industrial medical officers lasted two years but required attendance for only a day and a half a week. The department also appointed research fellows who were postgraduate science candidates for M.Sc. or Ph.D. degrees.

Prof. R. C. Browne, who occupies the Nuffield chair of industrial health at the University of Durham, felt that the chemistry graduate was usually the best equipped for the work, followed, in order, by physicist, engineer and doctor, though special risks, such as radiation, clearly affected this. Such graduates were in short supply at present.

During the discussion on the afternoon papers the question of payment for training was raised. Several speakers thought that industry, while willing to send employees on short courses lasting a week or two, might not be prepared to lose their services for a year. The suggestion that Government bursaries might be paid drew the reply that all the students taking a somewhat analogous course in public health engineering had been from overseas for several years past, supported by the World Health Organization or their own Governments ; no Treasury support was available for Britons. Other speakers considered it likely that bursaries would become available from industry.

The conference proceedings will be reported in full in the *Annals of Occupational Hygiene*.

C. N. Davies

# CLOSED CIRCUIT TELEVISION IN THE MEDICAL SCHOOL

A SYMPOSIUM on the applications of television in medical research and teaching was organized at the London Hospital Medical College during May 10–11 by the Medical Committee of the Scientific Film Association in collaboration with the Association for the Study of Medical Education. Since the 2-hr. demonstration of a land-line colour broadcast by a team from Guy's Hospital in 1957 (*Nature*, **181**, 91, 1958) no collective attempt had been made to evaluate and discuss the potential usefulness of closed-circuit television in medicine. This meeting is therefore a welcome sign that the universities are ready to concede that television need not necessarily be equated with mass entertainment. In fact, the conference was well timed, as many of the seventy senior representatives from British medical schools who participated are concerned with the planning of new buildings and the possible incorporation of closed-circuit television.

At least three schools are about to install such facilities and several others may shortly follow their example.

Apart from isolated *ad hoc* demonstrations by manufacturers of electronic equipment, and the somewhat elaborate presentations organized at congresses by a pharmaceutical firm, there is little practical experience in Britain. To ensure, therefore, that facts rather than opinions could be discussed, the organizers invited the co-operation of acknowledged experts in television engineering: on the use of television in a medical school in the United States, on research applications and on its uses in a military medical centre—both from the United States—and a surgeon in charge of television facilities at a German university.

While television has serious limitations, such as restricted resolving-power and relatively high cost, the conference has shown that television offers considerable advantages in a number of fields—with the obvious reservation that the usefulness of any device must depend on the ability and knowledge of the user, whether research worker or teacher. The main properties of television are: its ability to convert invisible radiation into visible images, its high sensitivity to light, electronically adjustable contrast, and above all, its ability to present instantaneously moving images, even of very small subjects, to an unlimited audience, while the camera may well be in a location too restricted or too dangerous for direct human observation.

Radiology makes full use of these properties. Small 'Vidicon' tube cameras can display enlarged pictures from the X-ray image converter. Similarly, large 'Orthicon' tube cameras equipped with systems of wide-aperture mirror lenses can reproduce the radiographic image from a life-size fluorescent screen with sufficient brilliance so that the radiologist need no longer work in the dark, and consultants and students can study simultaneously the same information on receiver screens in any number of different rooms. These methods make it possible to reduce the radiation received by the patient, so that the film records from the television screen can be used almost as a matter of routine for the study of processes within the human body. Image storage on special tubes, on ferro magnetic disks and on magnetic tape ('Video' tape) are now well beyond the laboratory stage, and the development in the United States of a really large television tube sensitive to X-rays will probably replace the use of the conventional fluorescent screen in the none too distant future.

Ultra-violet radiation, sufficient for direct photomicrography, will destroy biological tissues in a very short space of time, and similarly cine-micrographic studies of the retina would require an impracticable intensity of light. It is in these examples that the enlarging, intensifying and radiation-converting properties of television can be of value to research work. Camera tubes sensitive to ultra-violet radiation will produce images of the contents and behaviour of cells with greatly reduced radiation, and highly sensitive 'Orthicon' tubes can be used to record colour images of retinal blood vessels with light intensities which are well tolerated by the human eye. Tubes sensitive to infra-red radiation may be used instead of infra-red photography for the direct examination of the subcutaneous venous circulation.

A straightforward electronic method of superimposition makes it possible to display and record in accurate register on one receiver-screen two images from separate television cameras. Eye movements can thus be studied by superimposing the reflexion of a spot-light on an eye on to the image of the object which is being scanned by the subject.

Filming from the television receiver can also be used for selective studies of movements or behaviour. The television camera, with its automatic aperture compensation for changes in the intensity of light, can be operated from a distance by remote control. While the camera is in a relatively inaccessible or even dangerous location, the observer can aim and focus accurately by watching a television screen and record the action with a film camera in front of another receiver.

Applications in university teaching are obvious and numerous if it is remembered that television can ensure that every member of the audience can see equally as well as the demonstrator; the teaching of dental procedures is an outstanding example. The lecturer can use this enlarging device either in the classroom itself or in another room while he directs the demonstration with the help of a two-way communication system. The teacher can determine the area and degree of magnification of the subject to be displayed on a television projection screen or on receivers by adjusting the zoom lens on the camera from a small remote control panel. Chemical reactions, anatomical dissections or experiments under the microscope can be televised from within the lecture theatre itself, but other demonstrations, such as a psychiatric interview or a surgical operation, must take place elsewhere and are then relayed to the students and lecturer through closed circuit television.

Endoscopy, the exploration of body cavities, is perhaps a good example where television is equally applicable in both research and teaching. Here the television camera enables several research workers or a virtually unlimited number of students to study simultaneously what, until recently, could be seen by the endoscopist alone. Both in Britain and in the United States flexible bundles containing several thousands of very thin glass-fibres are being developed. Each fibre will, by internal reflexion, transmit a part of the image from a small lens to the television camera tube. The diminutive diameter and flexibility of these bundles make it possible to explore normal as well as pathological processes of organs inside the body which are not readily accessible to conventional optical endoscopes.

Like any other device, television should only be used where it is superior to other methods. It does not take the place of lantern slides or films, but there will clearly be occasions when an enlarged and detailed display of something which is happening now is likely to be more effective. Few films suit more than one teacher. They are too rigid, and it is impossible to modify what they present to suit the reaction of a particular audience.

Relatively inexpensive equipment, which is simple to operate and maintain, is now available, so that active experimentation should shortly replace the somewhat theoretical arguments on the assumed merits and demerits of television. Baylor University, where basic instruction on techniques in physiology are shown to students on television receivers in their individual laboratories, has demonstrated that television may contribute to better and more effective teaching, without in any way attempting to take the place of the teacher or individual practical experience by the student.

C. E. Engel

# THE FOURTH WORLD FERTILIZER CONGRESS

IT is generally believed that nitrogen is a key element in crop production. This is evident from the figures in Table 1, showing the yield in kilograms in different countries expected for an application of 1 kgm. of plant nutrient:

| Country | Crops in rotation | | | Permanent pastures | | |
|---|---|---|---|---|---|---|
| | N | P | K | N | P | K |
| Norway | 9 | 3 | 5 | 11 | 6 | 4 |
| Sweden | 14 | 11 | 7 | 14 | 11 | 7 |
| Denmark | 18 | 4 | 2 | 12 | 5 | 3 |
| U.K. | 16 | 5 | 5 | | | |
| Ireland | 20 | 8 | 8 | | | |
| Holland | 18 | 6 | 3 | 10 | 6 | 4 |
| France | 19 | 5 | 2·1 | | | |
| Germany | 19 | 8 | 4 | 9 | 10 | |
| Switzerland | 18 | 8 | 4 | 9 | 10 | 5 |
| Greece | 15 | 5 | 3 | | | |
| Italy | 11 | 3 | | 12 | 4 | 3 |
| Average | 16 | 8 | 4 | 11 | 7 | 4 |

In the *Oxford Economic Atlas of the World* (Oxford University Press, 1959) the following increased yields per kilogram of nitrogen are recorded:

| | Wheat | Rice | Potatoes | Grass (for hay) |
|---|---|---|---|---|
| Kgm. per hectare | 17 | 17 | 84 | 17 |

The Indian Council of Agricultural Research has reported that the average production of rice in India is ten times the amount of nitrogen applied. The United Nations Korean Reconstruction Agency has stated that 1 kgm. of nitrogen as ammonium sulphate produces 12–14 kgm. of brown rice and 14–28 kgm. of rough barley in South Korea. Moreover, 1 kgm. of phosphate as superphosphate can yield 4–18 kgm. of brown rice. In the United States large amounts of fertilizers have been applied in special cases and the results show a big response to nitrogen, but the responses to phosphate and potash are smaller. Doses in amounts larger than 200 lb. of nitrogen or phosphate or potassium per acre show a depressing effect in ordinary soils, but in soils of prairie lands naturally rich in humus, beneficial results are obtained with heavy doses of fertilizers.

Because of the importance of fertilizers in crop production, the world fertilizer industry is well organized by the International Confederation of Engineers and Technicians of Agriculture (C.I.T.A.) at the International Centre of Chemical Fertilizers (C.I.E.C.), Zurich. During May 9–12, the fourth World Fertilizer Congress, organized by the International Centre, met in Opatija on the Adriatic coast of Yugoslavia, under the presidency of Prof. S. Nikolic of Belgrade. Some 290 scientists, industrialists and technicians from twenty-eight countries met to consider six general reports and sixty-five special communications. At this Congress, besides French, English and German, Russian and Yugoslav were also recognized as official languages.

Prof. Nikolic gave an account of the soils of Yugoslavia and the application of fertilizers, micronutrients and organic matter. Prof. M. R. Braconnier, of Paris, reported on fertilizer production and consumption, and stated that in 1958–59, 8·75 million tons of nitrogen, 9·03 million tons of phosphate and 7·88 million tons of potassium were produced by the world fertilizer industries, and the average $N : P_2O_5 : K_2O$ ratio of fertilizers applied has shifted from 1 : 3·85 : 0·77 in 1900 to 1 : 1·03 : 0·9 in 1958–59. In Holland the ratio is 1 : 0·5 : 0·7. Prof. Y. Coic, of Versailles, discussed the adaptation of fertilizers by cultivated plants. Prof. L. Schmidt, of Darmstadt, discussed the experimental results obtained by compound fertilizers and trace-elements. The influence of irrigation on mineral fertilization was dealt with by Prof. L. Cavazza, of Italy. The application of radioisotopes was introduced by Prof. A. C. Schuffelen, of Holland; papers on work with phosphorus-32 carried out in Italy, Germany, Hungary, Poland and Yugoslavia were given.

The functions of light, temperature, acidity, coatings on fertilizers and humus in the absorption of nutrients by plants were discussed in several papers.

From a survey of crop production and fertilizer application in different countries, it appears that in countries not using large amounts of fertilizers the nitrogen response to cereals is very marked; the law of diminishing return is in operation in Holland, Belgium and Norway, where large amounts of nitrogen are applied. But in Japan, China and Taiwan, where composts and other plant and animal wastes are utilized along with fertilizers, better crop yields per unit nitrogen are still obtained. In the United States, yields of wheat and corn are increased by producing organic matter through rotations.

Approximately 1,000 million tons of cereals, 700 million tons of pulses, potatoes, vegetables, sugars, etc., are being produced annually in the world, and the world grassland production is about 1,600 million tons. Hence assuming the yield is 15 times the nitrogen application, the production of the world's food, fodder and fibre requires approximately 250 million tons of available nitrogen. It has been already stated that the industrial supply of nitrogen is only 8·75 million tons; legumes contribute 5 million tons and precipitation 7–10 million tons of nitrogen. Hence the world soil humus is the chief supplier of crop nitrogen. It is well known that the recovery of nitrogen by crops is smaller than that of phosphate and potash, chiefly due to loss of nitrogen as nitrogen gas in the processes of nitrate formation from manures and fertilizers, and this loss of nitrogen is retarded by organic matter and minerals. Experiments have shown that all nitrogenous fertilizers and manures when applied to land intensify the oxidation of soil humus due to the formation of nitrates in the soil. Organic matter such as straw, plant residues, grasses, etc., when incorporated in soils, not only improve the physical properties of the soil but also fix atmospheric nitrogen and protect the soil nitrogen and increase the humus capital and this is aided by different calcium phosphates. The world reserve of phosphate rocks is of the order of 21,000 million tons and its present utilization is 30 million tons annually. Moreover, the expanding world steel industry is supplying large amounts of basic slags rich in phosphate, lime, magnesia, manganese, copper, vanadium and other useful nutrients. Hence increased utilization of these cheap phosphates incorporated with organic matter could go a long way towards meeting the world-wide lack of nitrogenous fertilizers.

N. R. DHAR

## THE HAFFKINE INSTITUTE

THE annual report of the Haffkine Institute for 1959, which refers to the continued difficulty of recruiting qualified staff, includes lists of grants and research fellowships and scholarships as well as of papers published during the year*. Research activities in the Department of Antitoxins and Sera included the antigenic analysis of cholera vaccine and the use of submerged or shaken cultures for growing diphtheria toxin and pertussis vaccine. In the Department of Chemotherapy, the synthesis of compounds of possible anti-tubercular activity continued, including heterocyclic derivatives of thiourea and thiocarbanilide. Compounds with the *p*-nitrophenyl and/or dichloroacetyl groups attached to the pyrimidine, thiazole and pyrazole ring were also synthesized and tested *in vitro* against *Salmonella typhosa*, while other pyrazole and pyrazolene derivatives have been synthesized for examination as anti-convulsants. Two 1 : 3-disubstituted sulphonyl ureas have shown promise as antidiabetics.

The Department of Clinical Pathology and Diagnostic Reagents has finally identified *E. coli* from urine by sero type (preliminary) of 'O' antigen determination and is pursuing its investigations on the antigenic structure of the typhoid–paratyphoid group under partial anaerobiosis for possible application in preparing improved agglutinable suspensions. Besides epidemiological studies of enteric infection, it has continued its antigenic work on cholera vaccine, its investigations on otomycoses and, in collaboration with the Entomology Department and the Director's Laboratory, on the alimentary canal of the different rat-fleas with reference to the growth-promoting factors of some protozoa and bacteria. The Department of Entomology completed its studies on *Drosophila muris*, and started work on the morphological structure of the salivary glands of different non-poisonous snakes in comparison with the parotid glands of the poisonous snakes. Besides work on cholera autotoxin, the Department of Pharmacology continued its work on indigenous drugs, and has developed a new colorimetric method for determining 5-chloro-7-iodo- and 5: 7-diiodo-8-hydroxyquinoline by coupling with *p*-nitroaniline-2-sulphonic acid, and modified methods for determining *m*-aminophenyl in *p*-aminosalicylic acid have been examined as well as methods for determining 'Novalgin', 'Avil' and thymol.

In the Department of Virus Diseases the immunogenicity of viral vaccines was investigated with the view of standardizing testing procedures and work on the adaptation of locally isolated rabies street virus strains to embryonated eggs. The Biochemistry Section reports on preliminary methods of preserving tissues from cadavers, the screening of vegetable extracts for blood-group activity and the preparation of anti-*A* and anti-*B* serum, while the Department of Nutrition continued its nutritional evaluation of foodstuffs commonly consumed in Bombay State, and its investigations into the nutritive value of some leafy vegetables and their supplementary effect, as well as its work on fermented food[illegible] and on the effect of commercial sterilization on t[illegible] nutritive value of milk.

* Government of Bombay. Annual Report of the Haffkine Institute for the Year 1959. Pp. ii+74. (Bombay: Director, Government Printing and Stationery, Maharashtra State; London: High Commissioner for India, 1960.) Rs. 0·60; 1*s*.

## HOSPITAL IN-PATIENTS IN ENGLAND AND WALES

THE hospital in-patient inquiry for the years 1956–57 was organized jointly by the Ministry of Health and the General Register Office to provide statistics which will assist in the administration of the hospital services and contribute towards the knowledge of illness (morbidity) in the community*.

Information for the inquiry is supplied by hospitals, where the form is completed for one patient in every ten discharged, giving a confidential summary of the case record. Hospitals of all types except psychiatric take part in the inquiry which, since 1958, has covered virtually all hospitals in England and Wales. In 1956 and 1957, the years to which the present report relates, the inquiry covered 68·5 and 82·1 per cent respectively of all hospital discharges and deaths in England and Wales.

Apart from the main reference tables the report contains, for 1957, a series of tables devoted to duration of stay. This is related directly to bed-usage, and the figures should be of value for planning purposes.

Other features of the report are: a discussion of the statistical and other problems which arise in the interpretation of hospital morbidity data; some analyses according to the type of hospital in which patients were treated, and, for 'acute' hospitals, their size; a table showing age distribution for the 800 categories of the *Detailed List of the International Statistical Classification of Diseases*, and tables for six of the fully represented regions showing the local administrative area in which patients resided and the hospital group in which they were treated. These help to determine the 'catchment areas' of hospital groups.

Altogether, there were 3,485,000 discharges and deaths in 1957 in hospitals during the inquiry. The average duration of each spell of hospital care was slightly shorter than in 1955 or 1956, being 22 days for males compared with 24 days in each of the two preceding years and 20 days for females compared with 22; in half the cases the duration of stay was less than 10½ days.

During 1957 maternity cases stayed an average of 10 days after delivery compared with 11 days in 1955. The proportion of mothers discharged within 7 days of delivery increased from 7 per cent in 1955 to 13 per cent in 1957. 51 per cent of mothers stayed

* Ministry of Health; and General Register Office. *Report on Hospital In-Patient Enquiry for the two years 1956–1957*. Pp. vii+335. (London: H.M.S.O., 1961.) 18*s*. net.

8–10 days after delivery in 1957 and 36 per cent 11 days or more.

Children, aged 5–9 years, had the shortest average stay in hospital (11 days) and patients, aged 75 and over, the longest (45 days for men and 63 for women). Though this is mainly due to more chronic illness in older people, small children and older people stayed longer than older children and young adults for treatment of the same condition.

Of the patients aged 65 and more, women usually stayed longer than men; for circulatory diseases the average stay for men was 53 days and for women 72, and for injuries other than head injuries 29 days for men and 41 days for women.

In 'acute' non-teaching hospitals the average length of stay was shortest in medium-sized hospitals. The same was true at all ages and for both sexes, and for many specific diagnoses.

From data on the duration of stay, the number of hospital beds required by different groups of patients can be calculated. The number of beds required per 10,000 population increases greatly with the patient's age, ranging from 20·8 at ages 15–24 to 188·88 at ages 75 and more for men, and from 18·7 at ages 5–14 to 187·3 at ages 75 and more for women.

Of the 40·8 beds per 10,000 population used for male cases, 13 per cent were taken up by cases of respiratory tuberculosis; 7 per cent were occupied in treatment of malignant neoplasms, 13 per cent for cardiovascular diseases, 10 per cent for respiratory diseases and 11 per cent for digestive diseases. For females, 48·9 beds per 10,000 population were in use; 7 per cent of them for respiratory tuberculosis, 6 per cent for malignant neoplasms, 8 per cent for digestive diseases and 15 per cent for maternity cases.

## RESPONSE TO HOT ENVIRONMENTS

A REPORT* prepared by the Medical Research Council owes its origin to the concern felt by the Board of Admiralty regarding the thermal conditions to which men were exposed during the Second World War when serving in His Majesty's ships in tropical waters. This led, in 1944, to the appointment of a committee to inquire into and advise on the problems in this field. It was recognized from the outset that investigations would eventually have to be made in a tropical climate, and, in 1948, the Royal Naval Tropical Research Unit was established in Singapore under the joint auspices of the Admiralty and the Medical Research Council.

Before the establishment of the unit at Singapore, however, investigations were initiated in London at the National Hospital for Nervous Diseases. In the experiments carried out in London, the physiological effect on men wearing different types of clothing of exposure to high air temperatures was examined at different humidities and air speeds, both when the men were resting and when they were working. On the results of these experiments, for which the subjects had been artificially 'maximally acclimatized' by previous exposure to hot conditions in the laboratory, it was possible to base tentative recommendations concerning the conditions of warmth that were acceptable in ships at sea in tropical waters. The results also seemed to indicate that the 'effective temperature scale', which had been accepted for use as a measure of the severity of environment in ships, was misleading in certain respects. This led Dr. B. McArdle to devise a new index, the 'predicted four-hour sweat-rate' (P4SR), for the assessment of hot environments.

With the establishment of the unit at Singapore similar investigations were carried out. These confirmed largely the previous findings in London and, though they did not entirely support the criticisms of the 'effective temperature scale', they did demonstrate that the 'predicted four-hour sweat-rate' was an accurate and convenient measure of the severity of indoor hot-environments. The work at Singapore was, however, extended to compare the relative tolerance to heat of men who had been artificially 'maximally acclimatized' in the laboratory, with those who had been 'naturally acclimatized' by residence in a tropical climate. Investigations were also made of the stress imposed by radiant heat of long wavelength and by different rates of energy expenditure. Work carried out to determine the upper limits of warmth to be permitted in ships was extended to determine the upper limits that could be physically tolerated and the position of the 'comfort' zone. In addition, a number of physiological problems associated with these main lines of research was examined.

Now that the results of all the investigations in London and in Singapore have been brought together, it is clear that considerable additions to knowledge have been achieved. Much information has been obtained on the relative effects of various levels of air temperature, humidity, air speed, and radiant heat, and about the limits of heat which people can tolerate.

Answers have been provided to some of the practical problems of the Navy; the critical examination of a widely used scale of environmental heat-stress and the production and testing of a new index have improved and added to the techniques available for evaluating the severity of different climatic environments. As well as achieving these practical ends, this work has extended knowledge of the physiological mechanisms involved in the process of adaptation to hot environments and has indicated the direction for future research.

The report has been compiled by Dr. R. K. Macpherson with the assistance of an editorial board composed of Dr. T. Bedford, Dr. O. G. Edholm, Surgeon Captain F. N. Ellis, and Dr. N. H. Mackworth. It brings together much patient and arduous work by a number of service-men and civilians, and it is a fine example of how long-term investigations should be planned, organized and controlled. Many of its findings should be of interest to industrial organizations where hot processes are involved; managements in the new Indian steelworks should find much of value.

* Privy Council. Medical Research Council Report Series, No. 298. *Physiological Responses to Hot Environments*. Compiled by R. K. Macpherson. (An account of work done in Singapore, 1948–1953, at the Royal Naval Tropical Research Unit, with an appendix on preliminary work done at the National Hospital for Nervous Diseases, London.) Pp. xv+323. (London: H.M. Stationery Office, 1960.) 35s. net.

# SEA SURFACE TEMPERATURE IN COASTAL WATERS OF THE BRITISH ISLES

INVESTIGATIONS of the sea temperatures in British coastal waters have hitherto been neglected despite their value to workers interested in the ecology of the seashore and to meteorologists in connexion with fog forecasting. Mr. Lumb's short paper on the variations of these temperatures is therefore to be welcomed*.

The paper is really concerned with the whole of the shelf seas around the British Isles and not just with the waters within a few miles of the coasts. The typical winter and summer isotherm patterns, as derived from charts published by the International Council for the Exploration of the Sea, are first discussed. The winter pattern is explained in terms of cooling and vertical mixing in relation to the depth of the water column, but no mention is made of the part played by currents. In the North Sea, for example, the winter isothermal pattern is dominated largely by two tongues of warm water which are the result of currents bringing water into the sea from the Atlantic through the Straits of Dover and to the north of Scotland. To explain the summer pattern the work of Dietrich is used: this shows that stratification of the water column due to the absorption of solar radiation cannot take place in areas where the tidal streams are sufficiently powerful to provide a strong vertical mixing agency. In this connexion it is stated that the English Channel is nearly isothermal throughout the year. This is not so, as a thermocline develops in the western English Channel in summer.

The possibility of drawing quasi-synoptic temperature charts for five-day periods on the basis of sea-temperature observations made by light-vessels and a few selected ships is then examined, the typical seasonal isotherm patterns being taken as a guide to the course of the isotherms in places where the observations are scanty. Such charts are considered to be a possible aid to local weather forecasting. Five examples of the charts that can be produced by using this technique are given, and at first sight they appear to give reasonable pictures of the prevailing conditions. If, however, one goes beyond this paper and compares them with the corresponding monthly charts published by the International Council for the Exploration of the Sea, a few discrepancies are found even when allowance is made for the fact that the Councils' charts are based on a thirty-day period. They are probably due to different observational methods being employed. Indeed, the relative merits of the various ways of taking sea surface temperatures are a vexed question, but Mr. Lumb does not discuss the accuracy of the observations on which his charts are based. Further, there is some loss of detail, particularly as regards temperature gradients, in his charts compared with those of the Council, as the latter are based to a large extent on observations made by research vessels and merchant ships fitted with recording thermographs or sampling at close intervals. This loss might be important in so far as local forecasting is concerned. However, if charts are needed for forecasting purposes they must be produced rapidly, and the delay which usually occurs while oceanographic data are processed cannot be tolerated. Mr. Lumb is therefore wise to use only data which are readily available; but it would appear that if further investigations of this nature are to be carried out, then the marine meteorologists and oceanographers concerned should endeavour to standardize their methods and pool their data.

A. J. LEE

* Air Ministry: Meteorological Office. Scientific Paper No. 6. Seasonal Variation of the Sea Surface Temperature in Coastal Waters of the British Isles. By E. E. Lumb. Pp. ii + 21 (13 plates). (London: H.M. Stationery Office, 1961.) 3s. net.

# CORRECTION FOR EXTINCTION ERRORS IN CRYSTAL STRUCTURE ANALYSIS

By S. CHANDRASEKHAR and D. C. PHILLIPS*

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IT was shown recently[1,2] that it is possible to correct for primary and secondary extinction errors in the X-ray analysis of crystals by the use of plane polarized X-rays. If the incident beam is polarized with the electric vector perpendicular to the plane of incidence the integrated reflexion from a crystal suffering from primary or secondary extinction, or a combination of the two, is:

$$P'_{\perp} = \alpha|F|^2 - \beta|F|^4 \qquad (1)$$

to a good approximation when the proportional reduction of intensity by extinction ($\beta|F|^2/\alpha$) is not greater than about 25 per cent. If, on the other hand, the incident beam is polarized parallel to the plane of incidence, the polarization factor is $|\cos 2\theta|$, where $\theta$ is the Bragg angle, and since all other factors remain unchanged:

$$P'_{\parallel} = \alpha|F|^2\cos^2 2\theta - \beta|F|^4\cos^4 2\theta \qquad (2)$$

The true integrated reflexion for normal polarization:

$$P_{\perp} = \alpha|F|^2 = \frac{P'_{\parallel} - P'_{\perp}\cos^4 2\theta}{\cos^2 2\theta - \cos^4 2\theta} \qquad (3)$$

thus may be determined from measurements of $P'_{\perp}$ and $P'_{\parallel}$.

The theory has been verified experimentally in the determination of extinction in small crystals of rock-salt[2,3]. The main advantage of the technique is that

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it corrects for both primary and secondary extinction simultaneously in a crystal of any shape. Its principal limitation is that the equations become ill-conditioned for values of $\theta$ approaching 0°, 45° and 90°; the exact limits of applicability depend on the accuracy of the intensity measurements.

This article describes a simple apparatus which can be used conveniently in crystal structure analysis. The apparatus is shown in Fig. 1. Use is made of the fact that the angle $2\theta$ for the 311 reflexion of copper $K_\alpha$ rays by diamond is close to 90° (actually 91° 34' mean for $\alpha_1\alpha_2$). The reflected X-rays are therefore almost completely polarized with the electric vector perpendicular to the plane of incidence. The X-ray tube and diamond crystal are mounted on a disk which can be rotated about a horizontal axis collinear with the collimator of the diffractometer, in such a way that the reflected beam passes along the axis for every setting of the disk. The diamond is in the form of a plate (approximately 8 × 7 × 2·5 mm.) with (111) faces and the asymmetry of the 311 reflexion produces a broad beam convenient for use with small crystals completely bathed in X-rays. This beam is sufficiently strong for measurements of reflexions from a crystal mounted on the diffractometer to be made in the usual way by means of a proportional counter and crystal oscillation mechanism[4].

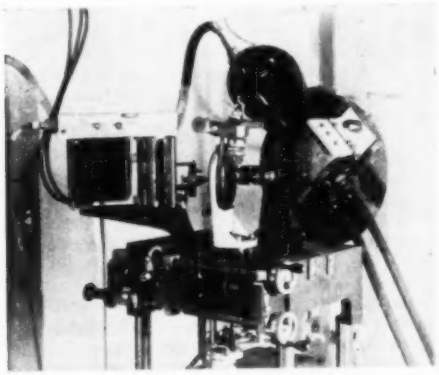

Fig. 1. Single-crystal diffractometer with apparatus for rotating plane of polarization of incident X-ray beam

The apparatus has been tested by performing Barkla's polarization experiment, using the 311 reflexion from small diamond crystals mounted on the diffractometer. The variation of integrated intensity with polarization angle was found to agree closely with the theoretical value and the ratio of the intensities of the two perpendicularly polarized components of the incident beam was estimated to be 0·0064.

The elimination of extinction errors by means of this technique has been tested in a study of reflexions from hexamethylene tetramine[5]. These crystals were chosen because some reflexions are known to suffer heavily from extinction[6], and because it seemed likely that liquid air shock treatment[7] would change the state of perfection of the crystals and enable a comparison to be made of corrected intensities from the same crystal with different amounts of extinction.

Fig. 2 illustrates the application of the method to one crystal with diameter about 0·05 cm. The ratio $p'_\parallel/p'_\perp$ for a range of reflexions is plotted against $2\theta$.

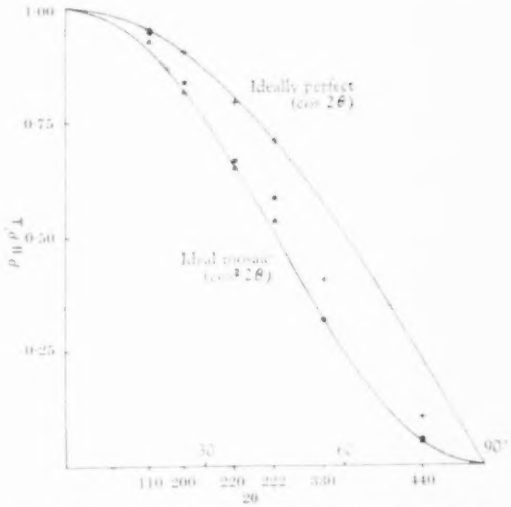


Fig. 2. $p'_\parallel/p'_\perp$ for reflexions from hexamethylene tetramine: ×, freshly grown crystal; ●, after one liquid air treatment; ▲, after two liquid air treatments

The upper curve is the theoretical curve for a perfect crystal, the lower that for an ideal mosaic. The measured values are those for a fresh crystal (crosses), and for the same crystal after one liquid air treatment (circles) and after a second treatment (triangles). Clearly strong reflexions from the fresh crystal have values appropriate to a perfect crystal, but the double liquid air treatment has reduced all the reflexions to values near those for an ideal mosaic. It must be remarked, however, that the strongest two reflexions 110 and 222 were found to be extinguished even after repeated liquid air treatment. Seven other crystals of different sizes were examined and in none of them was it possible to eliminate the extinction completely

Table 1. Measurements on Hexamethylene Tetramine, $C_6H_{12}N_4$: space group $I\bar{4}3m$; $a = 7{\cdot}02$ Å.

| $hkl$ | $p'_\perp$ (obs.) | $p'_\parallel$ (obs.) | $p'_\parallel/p'_\perp$ | Extinction (exp.) | $p_\perp$ | Theoretical: Ideally perfect $\cos^2 2\theta$ | Theoretical: Ideal mosaic $\cos^4 2\theta$ |
|---|---|---|---|---|---|---|---|
| **Freshly grown crystal** | | | | | | | |
| 110 $\theta = 8°\ 56'$ | 5·294 | 5·047 | 0·953 | Highly perfect | — | 0·9517 | 0·9057 |
| 200 $\theta = 12°\ 42'$ | 2·056 | 1·860 | 0·905 | Highly perfect | — | 0·9033 | 0·8159 |
| 220 $\theta = 18°\ 6'$ | 993 | 788 | 0·794 | Highly perfect | — | 0·8070 | 0·6512 |
| 222 $\theta = 22°\ 22'$ | 3·374 | 2·397 | 0·710 | Highly perfect | — | 0·7104 | 0·5047 |
| 330 $\theta = 27°\ 46'$ | 603 | 245 | 0·406 | 28 per cent | ·841 | 0·5660 | 0·3203 |
| 440 $\theta = 38°\ 24'$ | 1·529 | 162 | 0·106 | >30 per cent | — | 0·2286 | 0·0523 |
| **After liquid air treatment: Per cent** | | | | | | | |
| 110 | 22·148 | 20,947 | 0·946 | >50 | — | | |
| 200 | 3,654 | 3,057 | 0·837 | 12 | 4·160 | | |
| 220 | 1,898 | 1,264 | 0·666 | 6 | 2,020 | | |
| 222 | 10,290 | 6,010 | 0·584 | 24 | 13·556 | | |
| 330 | 805 | 255 | 0·317 | 0 | 805 | | |
| 440 | 2,664 | 149 | 0·056 | 7 | 2,862 | | |
| **After further liquid air treatment: Per cent** | | | | | | | |
| 110 | 28,400 | 26,355 | 0·928 | 20 | 35,800 | | |
| 200 | 4,000 | 3,260 | 0·815 | 0 | 4,000 | | |
| 220 | 1,953 | 1,270 | 0·650 | 0 | 1,953 | | |
| 222 | 12,220 | 6,535 | 0·535 | 11 | 13,692 | | |
| 330 | 817 | — | — | — | 817 | | |
| 440 | 2,792 | 147 | 0·053 | 0 | 2,792 | | |

Further liquid air treatment did not increase the intensities of any reflexions.

for these two reflexions by liquid air treatment. Nor was there any relationship between crystal size and the amount of residual extinction, indicating that primary extinction was probably taking place in these crystals[3]. These results again bring out the well-known fact that a crystal may behave as an ideal mosaic for a weak reflexion and yet show a high degree of perfection for a very strong one.

The measurements for this crystal are shown in Table 1, together with the integrated intensities corrected for extinction by the use of equation (3). These corrected values agree well for the different states of perfection of the crystal when the extinction is less than 25 per cent.

The complete set of measurements on this crystal took 8 hr. (with no breaks). There was evidence of a slight decrease in the intensities of reflexions from hexamethylene tetramine on prolonged exposure to air—approximately 6 per cent in 24 hr. No allowance has been made for this effect in the results presented here. Furthermore, the measurements have not been corrected for normal crystal absorption and they are, of course, on an arbitrary scale. The data have been corrected, however, for the small depolarization of the incident beam and the results for the seven other crystals, appropriately scaled, are in very good agreement.

We thank Dr. H. J. Milledge for the loan of the diamond plate, Dr. U. W. Arndt for help in setting up the counting system, Prof. R. King for his support, and finally, Sir Lawrence Bragg, whose interest and advice have been of the greatest value.

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# GIANT GRAIN GROWTH IN ALPHA FERRIC OXIDE

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AN investigation of the electrical properties of α ferric oxide revealed an anomalous resistivity-temperature curve for semi-spectroscopically pure iron oxide supplied by Johnson, Matthey and Co., Ltd. (Fig. 1, *b*). Roasted ferric oxide *per se* gives a linear plot over the same temperature-range (Fig. 1, *a*). The deviation shown by the curve *b* material is consistent with inhomogeneity of composition within the grains.

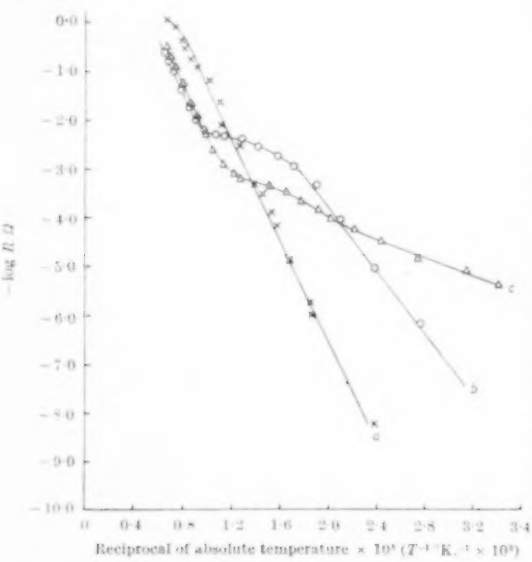


Fig. 1. The variation of resistivity of α ferric oxide with temperature: rectangular pellets, four probe. *a*, Ferric oxide from ferric nitrate by precipitation and roasting at 1,180° C. for 16 hr. in air; *b*, semi-spectroscopically pure ferric oxide 'as received'; roasted at 1,200° C. for 19 hr. in air; *c*, semi-spectroscopically pure ferric oxide treated as aqueous slurry with ultrasonic waves. 20 kc./s., 500 W. for 10 min.; roasted at 1,200° C. for 14 hr. in air

Attempts to remove the inhomogeneity included treatment of the material with ultrasonic waves prior to firing. A tuned stainless steel rod attached to an ultrasonic transducer (500 W., 20 kc./s.) was dipped into a slurry of 20 gm. semi-spectroscopically pure iron oxide in 200 ml. distilled water in a 'Pyrex' beaker. The slurry was agitated by slowly moving the beaker during the 10-min. treatment; the temperature rose to 40° C. The oxide was separated by decantation and dried in an air oven. Pellets were pressed without binder at 25 tons/in.² and fired in air at temperatures from 1,100° C. to 1,400° C.

The resistivity-temperature curve is modified by the treatment (Fig. 1, *c*). A polished section of this pellet showed giant grain growth throughout. The grains are distinguishable by anisotropy in polarized light and by etching with hydrochloric acid. Contrary to the usual pattern of crystallite growth, the inner grains are larger than those at the surface; the grain sizes in a pellet of unirradiated material are much smaller. Giant grain growth in ultrasonically treated material has been observed several times (Fig. 2*a* and 2*b*). The effect is not destroyed by pre-heating the ultrasonically treated material at 700° C. for 15 hr. before pelleting. After firing at 1,300° C. the unirradiated material shows hexagonal grains with straight sides, ranging from 10 to 40μ in diameter. The grains in the ultrasonically treated material show very irregular grain boundaries and contain many pores; the range in size is from 20μ for occasional grains near the periphery to 500μ for grains at the centre. The large grains show cracking both along grain boundaries and across grains, suggesting comparable strength of intra- and inter-crystalline material. The cracks probably occur during cooling, due to the anisotropy of the oxide. The temperature at which giant grain growth occurs in semi-spectroscopically pure iron oxide has been observed to vary from 1,200° C. to 1,375° C. The general appearance of the grains suggests rapid and irregular movement of the grain boundaries unhindered by pores.

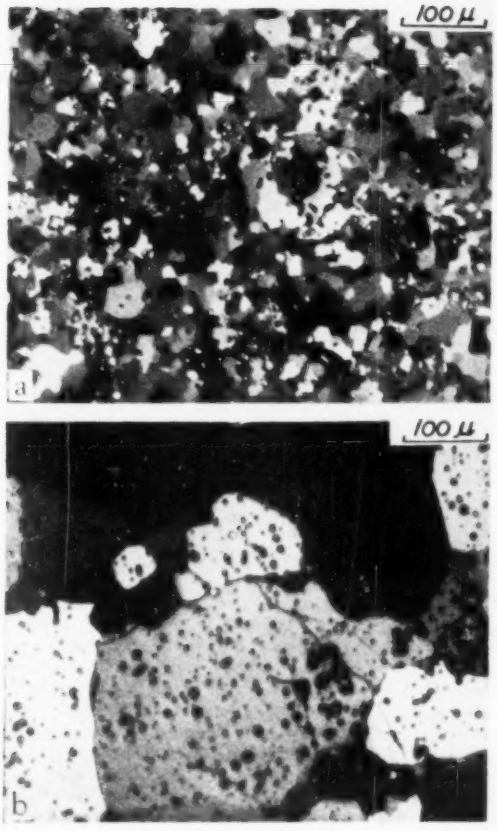


Fig. 2. Polished sections of pellets of semi-spectroscopically pure iron oxide fired in air at 1,300° C. for 15 hr.; incident polarized light. *a*, untreated; *b*, treated with ultrasonic waves before pressing and firing

Giant grain growth has not been observed in 'as-received' semi-spectroscopically pure iron oxide at temperatures up to 1,400° C., nor in the oxide slurried and dried without ultrasonic treatment.

Four possible explanations can be suggested. The first is that some impurity has been introduced during the ultrasonic treatment. The addition of 0·2 per cent titania to alumina causes giant grain growth[1], probably due to the formation of a eutectic melting below the firing temperature and assisting secondary crystallization. Spectroscopic analysis of semi-spectroscopically pure iron oxide gave: calcium, sodium < 0·1 per cent; silicon < 0·05 per cent; chromium, manganese, aluminium, titanium, lead, each < 0·02 per cent; nickel, copper, tin, each < 0·01 per cent; molybdenum < 0·005 per cent. No difference could be detected between the untreated and the treated material.

Two other explanations, that grain-growth is due to improved crystallite orientation, or to cleaning of the grain surfaces, are not easily evaluated. Cavitation will clean and probably de-gas the surface of a solid, will de-gas a liquid and produce very localized high temperatures. Chemical effects in aerated distilled water include the formation of traces of hydrogen peroxide. The iron oxide surface may be chemically modified, increasing the number of carriers (Fig. 1, *c*). Increased conductivity may also be due to the elimination of grain boundaries.

Finally, excessive growth might be attributed to a change in particle-size distribution. The fines in the slurry settle more slowly after ultrasonic treatment. Although ultrasonic waves in the 20 kc./s. range will de-laminate graphite and mica[2], it seems unlikely that comminution occurs at these wave-lengths. The fines probably result from the dispersion of agglomerates. Giant grain growth occurs in beryllia if the starting material has a wide particle-size distribution[3], though other factors are important[4]. Giant grain growth in iron oxide may be due to separation and dispersion of the fines throughout the material: it is observed in a temperature-range where grain growth becomes visible and where dissociation is incipient. Fine particles will be thermodynamically less stable at these temperatures and their resistance to re-orientation by an advancing grain boundary may be correspondingly reduced.

This work forms part of the research programme of Warren Spring Laboratory and is published by permission of the director.

We are greatly indebted to Mr. Owen-Roberts of Mullards, Ltd., for providing facilities for ultrasonic irradiation and for his helpful discussion; and to Mr. L. D. Muller of Warren Spring Laboratory for preparing the sections.

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# DERIVATIVES OF ISATIN BETA-THIOSEMICARBAZONE WITH ANTI-VIRAL CHEMOTHERAPEUTIC ACTIVITY AGAINST ECTROMELIA INFECTION

By Dr. D. J. BAUER and Dr. P. W. SADLER

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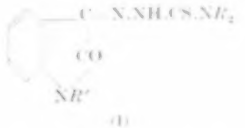
THE anti-viral chemotherapeutic activity of isatin β-thiosemicarbazone (I) in mice infected intracerebrally with neurovaccinia virus was investigated by Bauer[1], who found that mice infected with 100,000 *LD*50 of neurovaccinia virus could be protected against death by the repeated subcutaneous administration of the compound in doses of 2 mgm. Bock[2] also studied the effect of isatin β-thiosemicarbazone in mice infected intracerebrally with vaccinia, and made the additional observation that the compound had no antiviral effect in mice infected with ectromelia. In view of the close antigenic relationship between the two viruses, this finding was very surprising, and cast the first doubt on the generally

held view that an anti-viral compound would have to act by selectively affecting some host-cell system which was required for the multiplication of the virus. The observed fact that isatin β-thiosemicarbazone is active against vaccinia but not against ectromelia suggests that it is acting against the virus rather than against the host cell, which is the same in both infections. The force of this argument is not essentially reduced by the subsequent observation of Sheffield, Bauer and Stephenson[3] that isatin β-thiosemicarbazone is active against ectromelia virus in tissue culture, since the activity was very low and at the very limit of detectability. Bauer and Sadler[4] tested 19 derivatives of isatin β-thiosemicarbazone and related compounds for activity against ectromelia in mice, but none showed any evidence of activity. It is therefore of considerable interest that further work on the modification of the molecule of isatin β-thiosemicarbazone has now revealed a series of derivatives with high activity against ectromelia infection, and with little or no activity against vaccinia.




(I)

The compounds so far found to possess anti-ectromelia activity are all 4′ : 4′-dialkylthiosemicarbazones of isatin, N-methylisatin or N-ethylisatin. Dimethyl-, diethyl- and dibutyl-thiocarbamylthioglycollic acids were obtained by Jensen's method[5]. These, when heated in aqueous alkaline solution under reflux with excess hydrazine hydrate, produced the corresponding 4 : 4-dialkylthiosemicarbazides. The dibutyl compound, which is an oil, was converted to the hydrochloride by passing dry hydrogen chloride through its benzene solution. The 4′ : 4′-dialkylthiosemicarbazones (Table 1) were prepared by heating under reflux equimolar quantities of the isatin and reagent in ethanolic solution. In the case of the dibutyl derivatives, 50 per cent aqueous ethanol was used with the addition of one equivalent of sodium acetate. The melting points and analytical results for the 4′ : 4′-dialkylthiosemicarbazones are shown in Table 1.

Table 1. Analytical Results for 4′ : 4′-Dialkylisatin β-Thiosemicarbazones

| *R* | *R'* | Melting point (°C) | Formula | Required percentages C | H | S | Found percentages C | H | S |
|---|---|---|---|---|---|---|---|---|---|
| $CH_3$ | H | 232 | $C_{12}H_{14}N_4OS$ | 53·2 | 4·8 | 12·9 | 53·2 | 4·8 | 12·6 |
| $CH_3$ | $CH_3$ | 196 | $C_{13}H_{16}N_4OS$ | 54·9 | 5·3 | 12·2 | 54·7 | 5·0 | 12·4 |
| $CH_3$ | $C_4H_9$ | 193 | $C_{17}H_{24}N_4OS$ | 58·5 | 5·8 | 11·6 | 58·3 | 6·1 | 11·9 |
| $C_2H_5$ | H | 211 | $C_{13}H_{16}N_4OS$ | 56·5 | 5·8 | 11·6 | 56·5 | 6·0 | 11·7 |
| $C_2H_5$ | $CH_3$ | 129 | $C_{14}H_{18}N_4OS$ | 57·9 | 6·2 | 11·1 | 57·8 | 6·0 | 10·9 |
| $C_2H_5$ | $C_4H_9$ | 112 | $C_{18}H_{26}N_4OS$ | 59·2 | 6·6 | 10·5 | 59·4 | 6·8 | 10·7 |
| $C_4H_9$ | H | 151 | $C_{15}H_{20}N_4OS$ | 54·4 | 7·2 | 9·7 | 61·5 | 7·3 | 10·0 |
| $C_4H_9$ | $CH_3$ | 110 | $C_{16}H_{22}N_4OS$ | 62·4 | 7·5 | 9·3 | 62·3 | 7·7 | |
| $C_4H_9$ | $C_4H_9$ | 87 | $C_{20}H_{30}N_4OS$ | 63·5 | 7·8 | 8·9 | 63·1 | 7·9 | 8·8 |

The tests of anti-viral activity were carried out by two methods. In the first method, serial decimal dilutions of ectromelia virus (Sandom strain of pseudolymphocytic choriomeningitis virus) in the form of a suspension of infected mouse brain were inoculated intracerebrally or intraperitoneally in parallel in two series of mice of uniform weight, two groups of 6 mice being infected with each dilution; one series was treated with the compound under investigation and the other served as a control. The compound selected for test was inoculated subcutaneously twice daily for 5 days, the first dose being given some hours after infection. The mice were observed over a period of 14 days and the deaths were recorded. The results of five typical tests are given in Table 2. Isatin β-4′ : 4′-dimethylthiosemicarbazone (I; $R = CH_3$, $R' = H$) confers a significant degree of protection in mice infected with 100 *LD*50 of virus intracerebrally, and N-methylisatin β-4′ : 4′-dimethylthiosemicarbazone (I; $R = CH_3$, $R' = CH_3$) confers some protection against 1,000 *LD*50. With intraperitoneal infection the results were less regular, but the first compound nevertheless gave some protection against 1,000 – 10,000 *LD*50, and the second against 1,000 *LD*50. In the tests described so far the compounds were given at dose-levels of 25 and 50 mgm./kgm., but an antiviral effect was still

Table 2. Effect of Isatin and N-Methylisatin 4′ : 4′-Dimethyl Thiosemicarbazones in Mice Infected with Ectromelia Virus

| Compound | Dose of compound (mgm./kgm.) | Route of infection | Dose of virus (*LD*50) | Treated | Control |
|---|---|---|---|---|---|
| Isatin β-4′ : 4′-dimethylthiosemicarbazone | 25 | Intracerebrally | 1,000 | 6/6 | 6/6 |
| | | | 100 | 3/6 | 6/6 |
| | | | 10 | 0/5 | 6/6 |
| | | | 1 | 0/6 | 3/6 |
| | 25 | Intraperitoneally | 10,000 | 2/5 | 6/6 |
| | | | 1,000 | 5/6 | 6/6 |
| | | | 100 | 5/6 | 6/6 |
| | | | 10 | 0/6 | 5/5 |
| N-methylisatin β-4′ : 4′-dimethylthiosemicarbazone | 50 | Intracerebrally | 1,000 | 3/5 | 6/6 |
| | | | 100 | 1/5 | 6/6 |
| | | | 10 | 0/5 | 6/6 |
| | | | 1 | 0/5 | 3/6 |
| | 50 | Intraperitoneally | 1,000 | 0/6 | 12/12 |
| | 25 | | 1,000 | 3/6 | 12/12 |
| | 12·5 | | 1,000 | 4/6 | 12/12 |

Numerator, number of mice dying; denominator, number in group.

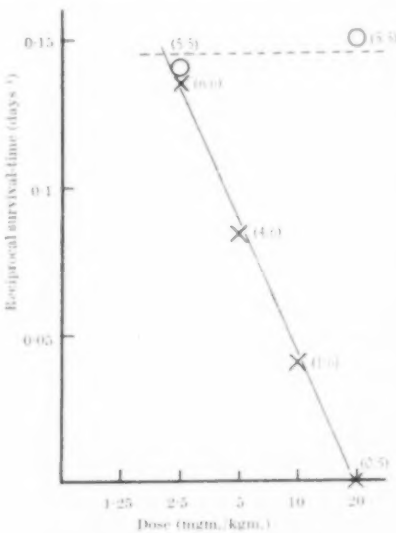



Fig. 1. Dose-response curve of antiviral chemotherapeutic effect of isatin β-4′ : 4′-diethylthiosemicarbazone in mice infected intracerebrally with 100 *LD*50 of ectromelia virus. ○, control; ×, treated. Numerator, number of mice dying; denominator, number of mice in group

observed with the N-methyl derivative at a dose-level of 12·5 mgm./kgm. as shown in the last test of Table 2.

In tests carried out by the second method, six groups of mice of uniform weight were inoculated intracerebrally with about 100 *LD*50 of ectromelia virus; the first and last groups were left untreated as controls and the remaining groups were treated with the test compound in doses increasing by multiples of 2 given subcutaneously twice daily for 5 days. The animals were examined for 14 days; the times of death were recorded to the nearest half-day and converted to reciprocals and the mean reciprocal survival-time for each group was plotted against the dose on a $\log_2$ scale. A result obtained with isatin β-4′ : 4′-diethylthiosemicarbazone (I: $R = C_2H_5$, $R' = H$) is shown in Fig. 1. The dotted line represents the mean response (reciprocal survival-time) obtained in the two control groups, and the continuous line has been fitted to the combined responses of the treated mice by the method of least squares. The responses do not differ significantly from linearity, and the anti-viral action of the compound can thus be represented by a linear dose-response curve, with complete protection against 100 *LD*50 of virus at a dose-level of 20 mgm./kgm., as represented by a reciprocal survival-time of zero.

In further tests carried out by one or both methods, marked activity against intracerebral or intraperitoneal infection with ectromelia virus was also found with isatin β-4′ : 4′-dibutylthiosemicarbazone (I: $R = C_4H_9$, $R' = H$), N-methylisatin β-4′ : 4′-diethylthiosemicarbazone (I: $R = C_2H_5$, $R' = CH_3$), N-methylisatin β-4′ : 4′-dibutylthiosemicarbazone (I: $R = C_4H_9$, $R' = CH_3$), and the three corresponding N-ethyl derivatives (I: $R = CH_3$, $C_2H_5$ or $C_4H_9$, $R' = C_2H_5$). Anti-viral activity of the same extent was also found in similar experiments with the Hampstead and Moscow strains of ectromelia virus. The compounds so far described had little or no activity against vaccinia infection in tests carried out by the same method.

The discovery of high activity against ectromelia in compounds of this type thus significantly extends the spectrum of anti-viral action of the isatin β-thiosemicarbazone derivatives, and gives reason for supposing that further modifications may lead to the acquisition of activity against other viruses.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# NEURAMINIDASE IN THE CHORIOALLANTOIS OF THE CHICK EMBRYO


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IN 1941, Hirst[1] and McClelland and Hare[2] described haemagglutination by influenza virus. The enzymic nature of this reaction was first suggested by Hirst[3], who showed that following agglutination of red cells, the virus eluted spontaneously, leaving the cells magglutinable by the same strain of virus; the liberated virus could agglutinate fresh red cells. Following the discovery that other viruses (including mumps and Newcastle disease) had similar activity, Burnet, McCrea and Stone[4] found that cells from which one strain of myxovirus had eluted were still agglutinable by certain other strains; the arrangement of virus strains in the order of their progressive action on cellular receptors was termed the 'receptor gradient'. In 1946, Burnet, McCrea and Stone[5] discovered in filtrates of *Vibrio cholerae*, a soluble factor, the receptor-destroying enzyme[6], which rendered red cells inagglutinable by myxovirus; the progressive action of this enzyme destroyed the agglutinability of the cells for different virus strains in a characteristic sequence—the receptor-destroying enzyme receptor gradient—and this differed in some respects from that of myxoviruses. Both viral and bacterial enzymes are now called neuraminidase[7] or sialidase[8], as their action has been identified as the hydrolytic cleavage of the glycosidic bond joining the keto group of sialic acid to D-galactose or D-galactosamine[9].

Myxoviruses are commonly grown in cells present in the chorioallantoic membrane (hereafter referred to as membrane) of chick embryos 10–12 days old. A previous attempt using biological methods to show the presence of neuraminidase activity in normal membrane was unsuccessful[7]. In this article we report the presence of neuraminidase activity in such extracts. The enzyme has been partially purified and concentrated, and its activity is described in biological and chemical terms. The possible relationship between this enzyme and the myxovirus enzyme is discussed.

*Detection of the enzyme.* The enzyme was detected by incubation of a sterile brei of membranes from 12-day-old embryos with excess sialyl lactose, a substrate of neuraminidase. The mixture was incubated (20 hr., 37° C., *p*H 5·7), samples taken at intervals and the amount of split product determined by the Warren test[8]. At a concentration of 1 mgm./ml. of sialyl lactose, the rate of release of split product, estimated as N-acetylneuraminic acid, was about 1·5 μgm./ml./hr.; the rate of action decreased slowly over the 20 hr. period. This activity was shown to be present in extracts heated to 56° for 30 min., but absent in extracts heated at 80° C. for 15 min.

*Age of the membranes.* The neuraminidase activity was found to vary with the age of the embryos from which the membrane was obtained. In one experiment, membranes from 8, 10, 12, 15, 18 and 19 day embryos (3 membranes of each group) were collected and ground with powdered 'Alundum' into *tris*-maleate buffer (0·1 *M*, *p*H 5·7, 2 ml./membrane). After clarification, the enzymic activity of each extract was determined (Table 1). In another experiment, twelve membranes from 19-day-old embryos were collected and extracted separately. All showed high levels of enzymic activity although the values showed considerable spread as would be expected. (Rate of release of N-acetylneuraminic acid (μgm./ml./hr.) = 18 ± 3·8 *S.D.*; average protein concentration = 4·0 mgm./ml.). Membranes of 19-day embryos from two different poultry farms showed similar high levels.

Table 1. Liberation of Split Product Estimated as N-acetylneuraminic Acid (N-ANA) from Sialyl Lactose (1 mgm./ml.) by Extracts of Avian Chorioallantoic Membrane

The reaction mixtures were incubated at 37° C. for 4½ hr. Protein was estimated by the method of Lowry *et al.* (ref. 24)

| Age of embryo (days) | Protein concentration of extract (mgm./ml.) | Release of N-ANA (mgm./ml./hr.) |
|---|---|---|
| 8 | 3·1 | < 1·0 |
| 10 | 2·7 | < 1·0 |
| 12 | 4·0 | 1·2 |
| 16 | 3·5 | 2·8 |
| 18 | 5·1 | 16·1 |
| 19 | 4·5 | 19·6 |

Addition of a membrane extract from 10-day-old embryos to a membrane extract from 19-day-old embryos did not significantly depress the enzymic activity of the latter. Membrane extracts from both 11- and 18-day-old embryos were found to contain approximately similar amounts of N-acetylneuraminic acid–aldolase, the enzyme which splits N-acetylneuraminic acid to N-acetylmannosamine and pyruvate[9]. The amount present was not sufficient to interfere seriously with the estimation of neuraminidase at *p*H values of 5·7 or lower.

*Bacterial sterility of membranes and extracts.* To eliminate the possibility that bacterial contamination of membrane or extract was responsible for the enzymic activity, four membranes from 19-day embryos were ground with 'Alundum' under aseptic conditions, clarified and enzyme assays carried out on each extract (37° C., 2 hr.; no antibiotics added). Each extract showed a high enzymic activity. Samples of the extracts before clarification and after the assay procedure were tested for aerobic and anaerobic bacteria, for fungi and for pleuropneumonia-like organisms. No growth of any organisms was detected over a period of 2 weeks incubation. In most work penicillin (100 units/ml.) and streptomycin (50 units/ml.) were included in the reaction media.

*Concentration and purification of the enzyme.* Membranes from 250 embryos (19 days old) were ground with 'Alundum' and the mixture extracted with *tris*-maleate buffer (*p*H 5·7, 0·1 *M*). The mixture was centrifuged and to the supernatant (about 1 litre) was added calcium chloride to a final concentration of 0·1 per cent (w/v). The solution was heated (56° C., 30 min.), centrifuged (70,000*g*, 10 min.) and ammonium sulphate added to the supernatant to a final concentration of 60 per cent (w/v). After standing (0° C., 16 hr.), the suspension was centrifuged (70,000*g*, 10 min.), and the precipitate dissolved in and dialysed against potassium phosphate buffer (0·1 *M*, *p*H 6·8). The solution was clarified by addition of protamine sulphate (0·3 gm.) and chromatographed on a column of hydroxyl apatite[10] (gradient 0·1 *M* – 2·0 *M* phosphate buffer, *p*H 6·8). The enzymically active fractions were pooled and concentrated to about 5 ml. The enzyme was purified about 50-fold in this way and was suitable for the tests described below.

*Properties of the membrane neuraminidase. Action on sialyl lactose.* Purified enzyme (0·5 ml.) was incubated with 10 mgm. of sialyl lactose (37° C., 16 hr.). The identity of the split products was established as follows. In the Warren test, the absorption spectrum (500–600 mμ) of the chromophore derived from the enzyme substrate mixture was identical with that given by crystalline N-acetylneuraminic acid. Following paper chromatography in butanol/pyridine/water (6 : 4 : 3), three spots corresponding in $R_F$ to sialyl lactose, N-acetylneuraminic acid and lactose were observed. In these experiments, more than 50 per cent of the sialyl lactose was split. The *p*H of optimum activity was about 4·5. The rate of action of the membrane enzyme was unaffected by 0·01 *M* ethylenediamine tetraacetate. $K_m$ at *p*H 4·4 was about $1 \times 10^{-3}$ *M*.

*Action on ovine submaxillary gland mucin.* Ovine submaxillary gland mucin was dissolved in the purified enzyme to a final concentration of 0·15 per cent (w/v) and the solution incubated (37° C., 16 hr.). Samples taken before and after incubation showed that (1) more than 60 per cent of the bound N-acetylneuraminic acid was liberated from the ovine submaxillary gland mucin. (2) The capacity of the treated ovine submaxillary gland mucin to inhibit haemagglutination by heated *WSE* virus[12] was abolished (inhibitory titre reduced from $1{\cdot}56 \times 10^5$ to < 50).

*Action on fowl red cells.* The agglutinability of the fowl red cells for the different strains of myxovirus was removed in the order shown in Table 2. This receptor gradient was not the same as that given by neuraminidase from *V. cholerae* determined under the same conditions. It is also different in several respects from the receptor gradient established by enzymic treatment of red cells with myxoviruses[3]. It is difficult, however, to obtain a satisfactory gradient following viral action when the technique used in the present work is adopted, so the virus results are not fully comparable to those obtained with soluble neuraminidases.

Table 2. Receptor Gradient of Fowl Red Cells treated either with Neuraminidase from the Chorioallantois of the Chick Embryo or with Neuraminidase from *V. cholerae*

| Source of neuraminidase | Receptor gradient | | | | | |
|---|---|---|---|---|---|---|
| Membrane | *MEL* | *NDV* | *Mu* *WSE* | *LEE* | *MIL* | |
| *V. cholerae* | *MEL* | *WSE* | *NDV* | *LEE* | *Mu* | *MIL* |

Serial two-fold dilutions of the purified enzyme and the crude enzyme from *V. cholerae* were allowed to act at *p*H 6·2 on 0·05 ml. amounts of washed packed red cells. The cells were then washed thrice with saline and their reaction to different strains of myxovirus tested (ref. 13).

## Discussion

The results show that the chorioallantois of the chick embryo contains an enzyme which, in many respects, behaves like bacterial and viral neuraminidases. Thus the membrane enzyme splits both sialyl lactose where the carbon atom 2 of N-acetylneuraminic acid is linked (α) to carbon atom 3 of galactose and also ovine submaxillary gland mucin where the carbon atom 2 of N-acetylneuraminic acid is linked (α) to carbon atom 6 of N-acetylgalactosamine[14]; it also abolishes the capacity of ovine submaxillary gland mucin to inhibit haemagglutination by heated influenza virus (although it has not been formally excluded that this may be due to a contaminating protease[15]) and destroys receptors of red cells for viral haemagglutination. In contrast to the neuraminidase from *V. cholerae*, the activity of both the membrane and viral neuraminidases are unaffected by ethylenediamine tetraacetate[16].

We have been very much aware of the possible objection that the neuraminidase discovered in the membrane is of bacterial origin. It should be pointed out that the enzyme content of unconcentrated extracts of membranes from 19-day-old embryos is equivalent to about 400 biological units/ml. of bacterial (*V. cholerae*) neuraminidase[17]. Heavy growth of an organism such as *V. cholerae* would be required to yield this amount of neuraminidase. Careful bacteriological examination failed to detect any micro-organisms in the membranes or in the incubated

extracts. We have not tested for latent viruses, but, for several reasons, this seems a very unlikely possibility.

The chief interest of this report is the finding for the first time of neuraminidase in vertebrate tissues. The possibility that it is present in all or most warm-blooded vertebrate cells cannot be excluded. One aspect which may be functionally significant is the demonstration that, as the fertile egg progresses to the stage where hatching of the embryo will occur, the neuraminidase content of the membrane increases ten- to twenty-fold. There is a suggestion here that the enzyme may play a part in preparing the membrane for its rather sudden loss of function as soon as the chick becomes air-breathing.

The possibility of a relationship between the membrane neuraminidase and the viral enzyme requires some consideration. At present it is reasonable to assume that the membrane enzyme is present in those cells which serve as host cells for the virus. The first question that arises is whether viral enzyme represents a component non-specifically adsorbed to the virus particle. This is most unlikely; the evidence is overwhelmingly in favour of the view that the enzyme is an integral component of the virus itself. Both serological[15] and chemical[19] analyses of purified myxoviruses support the view[20] that certain fractions of the myxovirus particle are very similar to components present in the normal host cell. Is the virus enzyme also in this category? Does virus invasion stimulate a change in cell metabolism which results in greatly increased neuraminidase production—a change that may in some way be analogous to the increase that takes place during the last days of incubation? In developing this suggestion we have to bear in mind: (*a*) that the enzymic activity of different myxoviruses shows a wide range of quantitative and qualitative differences; (*b*) that according to most authors the viral enzyme is related to the protein surface antigen *V*. To accommodate these findings, our hypothesis could take the form that the specific enzyme structure is determined by genetic information provided by the host but that this is incorporated into the virus under the influence of the virus genome, either during the intracellular synthetic process or during emergence from the host cell surface. If the specificity of the viral enzyme were of host origin this would help to explain why the myxovirus particle contains such a small proportion of ribonucleic acid[21]—an amount per virus particle of the same order as that present in much smaller viruses such as poliomyelitis[22], and presumably containing an equally limited amount of genetic information.

The present work does not, of course, exclude the possibility that the viral enzyme is as fully determined by the viral genome as any other component of the virus. It does, however, raise an important alternative. To choose between them will become easier if neuraminidases from the membrane and from representative myxoviruses are obtained in such a form as will allow a valid comparison of their physical, enzymological and serological properties.

While this work was in progress, Warren and Spearing[23] reported the presence of neuraminidase in commercial preparations of bovine and human serum glycoprotein. The enzyme was not detected in unprocessed plasma or serum. Their enzyme is stimulated by calcium ions and inhibited by ethylenediamine tetraacetate, so is different from the factor described in this report.

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# MECHANISM OF THE TRANSFORMATION OF THE POLYSACCHARIDE CAPSULE IN PNEUMOCOCCUS

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AFTER an interval of more than a year in the transformation of the heterologous polysaccharide capsule I found that the *R* form, which was obtained in our laboratory in 1957, and which prior to this had been very easily transformable into the encapsulated form of the type III pneumococcus with the aid of the transforming principle isolated from the same by use of the transforming medium in the presence of salts with univalent cations[1–3], is now not easily transformable when using similar conditions as before. Either it does not transform at all and remains in the *R* form, or changes

more or less massively into the encapsulated form of type II, that is, into the original parental strain. Only very rarely, and no longer under control or to a very small extent, if at all, is it transformed into the encapsulated form of pneumococcus of type III with the aid of the transforming principle isolated from this strain.

Ravin[4], using the strain *R*36A obtained originally in the laboratory by Avery *et al.* and successfully transformed in other laboratories[5,6] into various capsular states, found that the factor for antibiotic resistance was still transferable but not the capsular factor. I am of the opinion that the strain *R*36A may possess a gross deletion at one or more capsule-influencing loci.

Now the question arose whether in the course of preservation my *R* strain did not change to such a degree that it is unable to accept the transforming principle and to incorporate the relevant segment of deoxyribonucleic acid (DNA) into its genome or whether it had not been changed in another sense; on the other hand, whether my transforming principle had not been damaged (for example, by deoxyribonuclease) even though the isolation was always carried out in citrate medium and using all necessary precautions for the maintenance of its biological activity[7]. If this were the case, the damaged transforming principle would not function as a carrier of genetic information, that is, of information for the synthesis of the polysaccharide capsule of type III, but having been damaged would serve rather by its breakdown products to stimulate the synthesis of a non-specific DNA and thus also of a non-specific polysaccharide capsule in the recipient cell, in this case of type II.

I have in mind a similar effect to that described by Firshein and Braun[8], where the DNA, partly digested by enzyme and its products of cleavage, stimulates selectively the synthesis of the DNA in the *S* cells, in a mixture where there is a preponderance of *R* cells over *S* cells.

I examined first my *R* form, which had been originally fully avirulent, and found that, by testing in a solid medium or in glucose blood broth, the *R* form is not changed, but that in a selective medium, for example, in broth with anti-*R* serum, it is possible to intercept sporadically the maternal *S* form of type II both after 72 hr. of growth and *in vivo* when infecting mice.

The transforming principle was also checked. I investigated whether mild lesions of the polymeric molecule of the principle, due to small doses of deoxyribonuclease, would not result rather in a non-specific stimulation of the synthesis of the polysaccharide capsule of type II than in an induction of the synthesis of type III. I used a transforming principle (crude extracts of the DNA with 11 deproteinizations[7]) with a content of 2 γgm. DNA in 0·025 *M* veronal buffer *p*H 7·5 per 1 ml. of the medium and of deoxyribonuclease in a magnesium sulphate solution of a final concentration of 0·003 *M*. The transformation test was carried out either in the presence of sodium citrate of a final concentration of 0·01 *M*[9] or without it. The mixture of transforming principle and deoxyribonuclease with the citrate as well as without it had been activated for 15 min. at 30° C. and inactivated for 15 min. at 60° C. The control with the same content and with citrate in the medium had been neither activated nor inactivated. It was surprising to find that in the presence of deoxyribonuclease with a content of approximately 0·01 γgm. 1 ml. of the medium and with a lower content ($10^{-4}$–$10^{-5}$ γgm.) in the presence of citrate and in test-tubes, where the activation and inactivation had been carried out in the stated time-intervals, transformation of the *R* form into the *S* form of type III occurs regularly.

It is evident from Table 1 that the citrate added alone to the transforming medium inhibits the growth of the pneumococci and the test-tubes remain sterile. Among all variations of arrangements of components newly introduced into the transforming medium, transformation occurs solely in the presence of deoxyribonuclease in the concentrations already given in the presence of citrate and only when the mixture of the transforming principle and the deoxyribonuclease had been activated and inactivated, or only inactivated. If the deoxyribonuclease is left in the medium without inactivation in the presence of citrate, it prevents the transforming reaction.

Table 1. Effect of the Components added to the Transforming Medium

(Composition of the medium (ref. 2): beef heart infusion, 1 per cent neopeptone (Difco), 0·5 per cent sodium chloride, potassium chloride, $1·5 \times 10^{-4}$ *M*, 10 per cent anti-*R* serum), *p*H 7·6–7·8

| | |
|---|---|
| TP | *R* rarely *S* III |
| TP activ. and inactiv. | *R* |
| TP + $MgSO_4$ | *R* |
| TP + citrate | 0 |
| TP + $MgSO_4$ + citrate | *R* |
| TP + $MgSO_4$ + citrate + DNase | *R* |
| TP + $MgSO_4$ + citrate + DNase activ. | *R* |
| TP + $MgSO_4$ + citrate + DNase inactiv. | *S* III |
| TP + $MgSO_4$ + citrate + DNase activ. and inactiv. | *S* III |
| TP + $MgSO_4$ $3 \times 10^{-3}$ *M* + DNase + citrate activ. and inactiv. | *R* |
| DNA + $MgSO_4$ + DNase + citrate $10^{-4}$ *M* activ. and inactiv. | *R* |
| DNA + $MgSO_4$ $3 \times 10^{-3}$ + DNase + citrate $10^{-4}$ *M* activ. and inactiv. | *R* |

$MgSO_4$ in the final concentration 0·003 *M*; sodium citrate in the final concentration 0·01 *M*; transforming principle (TP) (2 γgm. DNA/ml.) in veronal buffer 0·025 *M*, *p*H 7·5, if DNase is present, otherwise in physiological solution; deoxyribonuclease (Light, and Hungarian lyophil.) in a concentration from $10^{-2}$ to $10^{-5}$ γgm. /ml. of the medium. The transformation was carried out in 2–3 control series with 1,000–3,000 cells of the recipient *R* cultures and the results read off after 16–96 hr. of growth in a liquid medium by sub-culturing twice daily on to glucose blood agar twice from each test-tube. The macroscopic identification was confirmed by agglutination with a homologous immune serum.

*R*, non-encapsulated form of the pneumococcus; *S* III, encapsulated form of the type III pneumococcus; 0, sterile growth.

The question has been posed whether a similar mechanism, that is, the mutual interaction of the DNA and the deoxyribonuclease with the participation of the blocking system, acts also normally in the processes of transformation. The problem of the penetration of the DNA as a high polymeric molecule into the cell still remains unknown. In experiments with newly isolated 9 new *R* strains, of which 12 single-colony cultures were chosen for the experiment, it was found that both the stable and the unstable strains are liable to transformation into the heterologous type, and that out of the twelve single-colony *R* cultures examined only 4 were transformed without deoxyribonuclease; the remainder only when it was present. As the experiments were carried out with two transforming principles obtained from the isolation of the same culture of the pneumococcus of type III, differing from each other only in age by 3 hr. (6 and 9 hr. culture) it was ascertained that it was possible to transform without deoxyribonuclease the newly gained strains only when the principle isolated from the younger culture was used.

It is evident from the experiment that the process of transformation of the heterologous polysaccharide capsule is by no means simple. There exist mutual interactions between the physiological state of the recipient cell and the biological activity of the transforming principle, certainly depending on the

structure of the DNA, which depends again on the physiological state of the cells from which the transforming principle had been isolated. It is possible that the deoxyribonuclease which those who work with pneumococci have always strived to eliminate by using only a small number of recipient cells, to avoid the depolymerization of the DNA by the deoxyribonuclease which is liberated by those cells, plays an active part in the transformation, even though the deoxyribonuclease in minimal concentration, acting only within a certain time-span, is blocked moreover by citrate (or another blocking system). Details of this work will be published in *Folia Microbiologica*.


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## PROTEINS OF HEN'S EGG YOLK

IN a recent communication on the proteins of the plasma and egg yolk of the hen, Schjeide and Urist[1] remark that much confusion exists in "the nomenclature, chemical constitution and physical orientation" of these proteins. As the portion of their analysis dealing with current knowledge of the yolk proteins is limited in scope and somewhat speculative another view of the biochemistry of yolk proteins is offered here. While this article is based largely on experience in this Laboratory, I do not regard these findings as absolute and irrefutable facts; but the criticisms of this work implicit in the article by Schjeide and Urist do not suggest to me any radical revision of our views.

Fevold's[2] review of ten years ago provides an adequate reference to earlier investigations. At that time, four proteins had been isolated from egg yolk, although it was recognized that none of these had been shown to be homogeneous by modern criteria. Recently, Schjeide and Urist[3] detected, by ultracentrifugation, both a floating and a sedimenting component in the fluid portion of egg yolk and two more sedimenting components in a solution of the solid granules. The nomenclature used infers that these components differ from the known fractions of egg yolk, although most of their distinguishing properties appear to be the same. Similar flotation patterns of the low-density fraction (about 90 per cent lipid) have been published[4], and this fraction has been shown[5,6] to yield lipovitellenin (about 40 per cent lipid) on ether extraction. They[3] called the sedimenting component in the fluid fraction 'ovalbumin' and defined it as "one of the components of livetin", a statement that does little to clarify nomenclature, but quite correctly suggests that there is more than one livetin. In the granule fraction their phosphoprotein $X_1$ is said, indirectly, to be an impure form of Mecham and Olcott's[7] phosvitin (containing 9·7 per cent phosphorus) and that their lipoglycoprotein $X_2$ "seems to be synonymous with" the $\alpha$-lipovitellin of Sugano[8], or lipovitellin. Evidently Schjeide and Urist have detected four ultracentrifugal components corresponding to the four proteins previously isolated and described by other workers. This is in general agreement with earlier reports[4,9] which, depending on the conditions employed, indicate the resolution of three to five ultracentrifugal components in solutions of egg yolk.

The ultracentrifuge, however, cannot resolve all the yolk proteins shown to be present in substantial proportions by electrophoretic analysis. Sugano's[8] patterns suggest at least five components in ether-extracted egg yolk, and Bernardi and Cook[10] identified six in the sedimenting material from which the floating fraction, containing lipovitellenin ($\beta$-lipovitellin of Sugano), had been removed. These components have all been isolated and characterized[7,10–16] as to molecular weight, N-terminal amino-acids, as shown in Table 1; and some by amino-acid composition or other properties. Clearly, seven proteins are present in egg yolk, and there are indications that some of these are not homogeneous. Consequently, one or more of Schjeide and Urist's four ultracentrifugal components must have contained more than one protein.

The procedures developed in this Laboratory for the isolation of these proteins (Table 1) are typical of widely used biochemical techniques. The usual precautions were taken at all stages with respect to temperature and other conditions. Naturally, some of the steps must be repeated to obtain homogeneous preparations, and some may be omitted; for example, the chromatographic procedure can be used directly to obtain certain proteins. Schjeide and Urist[1,3] term these 'chemical' procedures and state that it is 'obvious' that at least phosvitin so obtained is a derived protein that loses most of its calcium, often part of its phosphorus, and may even be derived from breaking the 'phosphoprotein backbone'. In support of these statements they point to the lower sedimentation coefficient of our isolated preparations. Phosvitin is a polyelectrolyte that occurs in egg yolk as an insoluble salt, which is converted partly to the sodium salt with a loss of calcium when dissolved in sodium chloride solutions, the commonly used solvent also employed by Schjeide and Urist for their sedimentation experiments. They have not demonstrated the loss of phosphorus but rather the reverse, since they state[1] that their $X_1$ phosphoprotein and phosvitin, prepared according to Joubert and Cook[11], had the same phosphoserine content. Later they say that both phosvitin and lipovitellin are 'known' to be altered to a greater extent than other proteins isolated from physiological fluids, regardless of the method employed for their isolation. This may be so; but, as no evidence is presented to support this generalization, the reader must decide *quaecumque vera*.

With a knowledge of the N-terminal amino-acids of the several proteins[15,16], the protein phosphorus content of $\alpha$- and $\beta$-lipovitellin (Burley, R. W., and Cook, W. H., unpublished work) (Table 1), and further physical determinations[10,14], it has been possible to estimate the composition of the ultracentrifugal components in solutions of the high-density fraction of egg yolk. Clearly, six proteins are present in this

Table 1. Preparative Procedures and Properties of Egg Yolk Proteins

| Preparative procedures Egg yolk dissolved in 0·45 *M* magnesium sulphate; centrifuged at high speed | Designation | Characteristic properties | | | | Refs. |
|---|---|---|---|---|---|---|
| | | $M \times 10^{-3}$ | Principal *N*-terminal amino-acids | Lipid content (per cent) | Protein phosphorus content (per cent) | |
| Low-density floating fraction; no known method of fractionation | This fraction yields lipovitellenin (about 40 per cent lipid) on ether extraction | 480 | Arg, Lys | 90 | < 0·5 | 5, 6, 15 |
| High-density sedimenting fraction | | | | | | |
| Precipitated at 0·15 *M* mag. sulphate | Phosvitin | 3·6 | Ala | | 9·6 | 7, 11, 16 |
| Precipitated at 0·05 *M* mag. sulphate (α- and β-forms separated by column chromatography) | α-Lipovitellin | 40 | Arg, Lys | 20 | 0·50 | 9, 10* |
| | β-Lipovitellin | 40 | Arg, Lys | | 0·27 | 14, 15* |
| Soluble in 0·05 *M* mag. sulphate | α-Livetin | 8·0 | Arg, Lys | 0·1 | < 0·10 | 12, 16 |
| Soluble in 37 per cent sat. ammonium sulphate (α- and β-forms separated electrophoretically) | β-Livetin | 4·2 | Lys + 2 others | | | |
| Precipitated by 37 per cent sat. ammonium sulphate | γ-Livetin | 15 | Ala | 0·5 | 0·03 | 13, 16 |

* Also unpublished work by Burley, R. W., and Cook, W. H.

fraction, although they sediment as only two major components ($S_1$ and $S_2$) in 5 per cent sodium chloride. The faster sedimenting $S_1$ component is a complex of α- and β-lipovitellin with phosvitin, plus an aggregated form of γ-livetin, a protein which has been isolated and described[12], but which is not resolved from this complex by ultracentrifugation in 5 per cent sodium chloride. After precipitation by dilution, the $S_2$ component is absent and other analyses show that α-, β- and γ-livetin and part of the phosvitin are removed. Evidently γ-livetin does not interact strongly with the lipovitellins, as originally suggested[9]. The original $S_1$ component obviously contains phosvitin, since its protein phosphorus content approaches 2 per cent, and is only reduced to about 1 per cent after repeated precipitation from 5 per cent sodium chloride by dilution, a result in agreement with the protein phosphorus content reported by earlier workers who used this method[17]. Since this is twice the phosphorus content of the mixed lipovitellins prepared from magnesium sulphate solutions[6], or by chromatography (Table 1), this complex, which sediments as one component, must contain about 5 per cent phosvitin of 10 per cent phosphorus content. In fact, the protein phosphorus contents reported[14] for isolated α- and β-lipovitellin are now known to be high owing to the difficulty of removing phosvitin from lipovitellin by hydroxyapatite chromatography, and more accurate values are reported (Burley, R. W., and Cook, W. H., unpublished work) in Table 1. Schjeide and Urist[1] state "that no significant amount" of phosvitin is complexed with lipovitellin. A complex containing 5 per cent phosvitin is not likely to be detected by sedimentation, but this amount is highly significant analytically. These authors do not report the results on which their conclusion is based, but it seems doubtful that the partition-cell procedure would yield their $X_2$ (lipovitellin) free of $X_1$ (phosvitin).

In alkaline solvents a third component of about 7 *S* (not 4–5 *S*) appears in the high-density fraction and increases in amount as the *p*H is increased. At *p*H 7·6 (pattern reproduced as Fig. 2 by Schjeide and Urist), this component is predominantly a non-aggregated form of γ-livetin[14]. At higher *p*H values a second component of about 7 *S* also appears in lipovitellin solutions now known to be free of phosvitin and γ-livetin by protein phosphorus and end-group analyses. We have also used the method of Schmidt, Bessman, Hickey, and Thannhauser[18] employed by Schjeide and Urist for isolating the yolk granules, and found that the three livetins are absent from solutions of the granule proteins. Without the livetins, phosvitin and the lipovitellins are clearly evident as two components in neutral solvents, but in alkaline solvents a third component of about 7 *S* is also present.

Clearly, the additional ultracentrifugal component observed in alkaline lipovitellin solutions is not γ-livetin. Before the present criteria were available, we erroneously called this 7 *S* component γ-livetin, since it had a similar sedimentation-rate, was reduced in amount by repeated precipitation[9], and had a type of dependence on *p*H suggesting that lipovitellin contained two distinct proteins. Moolenaar[19] also observed this second component in lipovitellin at *p*H 7·8 or higher and correctly called it a sub-unit of lipovitellin. The identity of this 7 *S* component was clarified by the work of Bernardi and Cook[10,14,20], who found that lipovitellin had two electrophoretic components, α- and β-, separated them by chromatography, and established that both forms dissociate reversibly into two sub-units in alkaline solvents. Both lipovitellins behave as *p*H-dependent reversible association-dissociation systems, but β-lipovitellin dissociates at a lower *p*H than α-lipovitellin. These findings explain our earlier observations indicating that lipovitellin contained two proteins.

I cannot reconcile these results with those reported by Schjeide and Urist[1]. They claim discovery of an alkaline breakdown product of lipovitellin of 4·5 *S* and suggest this may be the second component called γ-livetin by Joubert and Cook[9]. Evidently they have observed the second component reported earlier[9,19], and correctly identified by Moolenaar[19]; but they do not describe its properties. They do report the isolation of a trailing component which was found to be the natural form of phosvitin containing 10 per cent phosphorus. Clearly, this was not the 7 *S* component observed in alkaline solutions of our phosvitin-free lipovitellin. In fact, it appears that these workers isolated their trailing component from a solution of the granule proteins in 10 per cent sodium chloride, a solvent in which the sub-unit of

lipovitellin does not exist. Alternatively, if they did use an alkaline solvent, they should have resolved three components in the granule proteins. Their results appear, therefore, to have no bearing on the identification of the 7 *S* component under discussion.

Since lipovitellin, the classical lipoprotein of egg yolk, has now been fractionated, it is desirable to clarify nomenclature. Although the three fractions that have been characterized are, correctly speaking, lipoglycophosphoproteins, in this Laboratory we have continued to use modifications of the older, simpler names, α- and β-lipovitellin, and lipovitellenin; corresponding names for the three lipid-free protein moieties are provided by omitting the prefix 'lipo'. Our α- and β-lipovitellin are not identical with those so designated by Sugano[8], who used ether-extracted egg yolk and identified his α- and β-components as purified forms of lipovitellin and lipovitellenin, respectively. In our work lipovitellenin was removed by centrifugation and the terms α- and β- used to describe the two electrophoretic components of lipovitellin proper. Our α- and β-forms are not resolved by ultracentrifugation in sodium chloride solutions, but the parent molecules and their dissociated sub-units can be resolved in alkaline solvents. Lipovitellin may therefore occur in at least four forms.

Since the second component in lipovitellin solutions is a dissociated sub-unit and not γ-livetin, the molecular weights observed in sodium chloride solutions are now quite consistent[4,9,14]. Those reported by Joubert and Cook[9,11], however, are subject to correction for a computational error affecting the diffusion coefficient, which increases all those reported by about 15 per cent. The correct values have been published[14]. The phosvitin–lipovitellin complex precipitated from, and examined in, sodium chloride solutions had $M = 4{\cdot}0 \times 10^5$ by light scattering[4], and $4{\cdot}1 \times 10^5$ by sedimentation-diffusion[9]. At *p*H 9·0 the presence of 10 per cent or more of the dissociated sub-unit reduced the molecular weight of lipovitellin to $3{\cdot}7 \times 10^5$ (corrected value), but in sodium chloride solutions both α- and β-lipovitellin had $M = 4{\cdot}0 \times 10^5$ (Table 1)[14]. Since the lipovitellin–phosvitin complex contains only about 5 per cent phosvitin, its molecular weight would not be expected to differ, beyond experimental error, from that of undissociated lipovitellin.

The molecular weights of $X_1$ and $X_2$ proteins are reported by Schjeide and Urist[2] to be $7{\cdot}7 \times 10^4$ and $2{\cdot}0 \times 10^5$, respectively, which differ considerably from our values of $3{\cdot}6 \times 10^4$ and $4{\cdot}0 \times 10^5$ for phosvitin and lipovitellin. They suggest that our phosvitin was degraded, but do not advance a specific reason for the discrepancy in the estimated size of lipovitellin. An evident explanation is that their $X_2$ contained $X_1$, since the latter could not have been completely removed by separation in a partition cell. They found that $X_1$, $X_2$ and serum albumin all showed comparable boundary-spreading in the ultracentrifuge, but do not report diffusion coefficients. The molecular weights were evidently calculated from the sedimentation coefficients and the "reasonable assumption" that the $X_1$ and $X_2$ proteins have an axial ratio comparable with serum albumin. This assumption, however, is neither reasonable nor adequate for the estimation of molecular weights. It is not reasonable for phosvitin, since the results of Joubert and Cook[11] show that this protein and its soluble complexes with calcium all had frictional ratios far larger than that of serum albumin, and no evidence is presented to show that $X_1$ differs in this respect. The assumption is inadequate, since this calculation also assumes that both $X_1$ and $X_2$ have the same partial specific volume as serum albumin, which is neither in accord with expectation (composition) nor experimental observation[9,11]. These considerations also have a bearing on their conclusions[2] regarding the relative sizes of their $X_1$ and $X_2$ proteins in egg yolk and hen plasma.

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Dr. Cook's article constitutes an excellent summary of the large amount of work that he and his associates have carried out on the subject of egg yolk proteins, and brings into focus several crucial points where disagreements seem to exist among workers in the field. We shall take these up, but first would like to recapitulate the reasons why we submitted our original communication[1].

Basically, we were concerned with what seemed to be a general failure to recognize that the chemically derived phosvitins and lipovitellins of serum and egg yolk may be considerably different from these proteins as they occur in the native state. Secondly, we wished to explain our reasons for employing the serum and egg yolk $X_1$–$X_2$ nomenclature, and wished to caution against use of terms already ascribed to the chemically derived proteins when referring to the 'native proteins' as they might be resolved during gentler procedures of ultracentrifugation, etc. Thirdly, we wished to explain our view that serum $X_1$-phosphoprotein and serum $X_2$-lipoglycoprotein do not exist together as complexes in serum and that egg yolk $X_1$-phosphoprotein and egg yolk $X_2$-lipoglycoprotein are not present as complexes in 5 per cent sodium chloride at neutral *p*H as suggested by Cook and by Common and co-workers[2]. We wished, further, to make it clear that the reasons for the non-existence of such complexes constitute some of the most important facets of our understanding of the nature

and role of those unique proteins adapted to the sustenance of the embryo bird, reptile and amphibian.

In the preceding article Dr. Cook has reopened certain of these issues. For the sake of brevity, we shall mention only a few points on which we still differ:

(*a*) We have not changed our view that both phosvitin and lipovitellin obtained chemically as described by Joubert and Cook in 1958 (ref. 3) differ in certain respects from the ultracentrifugally resolved $X_1$ and $X_2$ proteins and are probably (at least in the case of the phosphoprotein) less 'physiological'. (i) Phosvitin definitely lacks most of the calcium which was originally associated with this molecule, and because of its lower sedimentation constant appears to be either (or both) broken or of increased axial ratio. (The loss of calcium, in its simplest terms, would result in only a 5–7 per cent reduction in molecular weight.) (ii) Joubert and Cook[3] have shown that the correct molecular weight for phosvitin is about 36,000. Thus, it appears that phosvitin obtained chemically is at most only half the molecular weight of its counterpart obtained more simply by dissolution of the yolk granules with 10 per cent sodium chloride followed by differential ultracentrifugation. Our estimation of the molecular weight of egg yolk $X_1$-phosphoprotein (77,000) was based on the premise that the phosphoprotein was as globular in shape as albumin. If a greater axial ratio actually obtains, the molecular weight of $X_1$-phosphoprotein is even greater than indicated by our original estimate. (iii) With respect to lipovitellin, Joubert and Cook[3] have, themselves, pointed out that, as originally obtained, it was not a pure fraction.

(*b*) Another of the views that has been strictly maintained by Dr. Cook and co-workers is that their faster sedimenting $S_1$ component of whole egg yolk in 5 per cent sodium chloride (our $X_2$-lipoglycoprotein) is a complex of the 'alpha' and 'beta' lipovitellins with phosvitin. (i) It has been our experience that the association of phosphoprotein with lipoglycoprotein (as by dilution or change in *p*H in the presence of sodium chloride) results in macro-complexes possessing sedimentation constants considerably in excess of *S* 10. Even if a complex of only one molecule of phosvitin per molecule of 'alpha' or 'beta' lipovitellin were postulated—such a physical orientation should produce a detectable difference in the rate of sedimentation as compared with phosvitin-free lipovitellin. (ii) Dr. Cook states specifically that "the $S_1$ [our egg yolk $X_2$] component obviously contains phosvitin since its protein phosphorus content approaches 2 per cent and is only reduced to about 1 per cent after repeated precipitation from 5 per cent sodium chloride by dilution".

Two misconceptions are evident here: in the first place, the $S_1$ material (*S* 10) as present in the preparatory ultracentrifuge tube necessarily contains phosvitin since the $S_1$ deflexion simply defines the boundary of a molecular species which is sedimenting through a medium containing sodium chloride, phosvitin, etc. The material causing the $S_1$ deflexion cannot be isolated from the centrifuge tube alone. Only a mixture of this component together with the other materials in the medium through which it is passing can be obtained.

In order to ascertain which component in the centrifuge tube contains phosphorus or calcium (and hence phosvitin) one can proceed indirectly as follows: the mixture of proteins is centrifuged in a partition cell for the preparatory ultracentrifuge[4] and is then partitioned into several vertical sections. Differing amounts of the various proteins in the mixture are present in each section, their concentrations being functions of their rates of sedimentation. The content of each section is ascertained by analytical ultracentrifugation and analysis for protein phosphorus. One can now determine by inspection whether the phosphorus rises in proportion to the deflexion caused by a given protein component. Neither protein phosphorus nor calcium increases detectably when the $S_1$ (our $X_2$) component is present in greater concentration in any particular segment[5].

Secondly, our experimental results[5] indicate that the reason the $S_1$ (our $X_2$) component is precipitated with dilution is that large complexes form between $X_1$-phosphoprotein on one hand, and $X_2$-lipoglycoprotein on the other. Hence, repeated precipitation should not result in complete elimination of phosvitin phosphorus from lipovitellin prepared by the method of dilution.

(iii) The occurrence of a precipitate is apparently due to the many negative charges appearing on the $X_1$-phosphoprotein (following the removal of calcium by dilution) reacting with positive charges on the $X_2$-lipoprotein. So long as these two molecules are present in a neutral medium of high ionic strength such as 5 per cent sodium chloride, the complexes do not form, even when much of the calcium has been removed. We have successfully separated each of these molecules ($X_1$ by differential ultracentrifugation and $X_2$ by extraction from frog larvæ cells (tail-bud stage) in which $X_1$ is absent[6] and have found that they are each perfectly soluble in distilled water by themselves. However, mixing the two clear solutions will cause the formation of a copious precipitate.

(*c*) It cannot be reasonably disputed that the following sedimentation differences exist when egg yolk and serum components are centrifuged in the same 5–10 per cent sodium chloride medium: egg yolk $X_1$ sediments faster (*S* 4·7) than phosvitin (*S* 3·5); serum $X_1$ sediments faster (*S* 8–9) than egg yolk $X_1$ or phosvitin derived from serum (*S* 3·5); serum $X_2$ sediments faster (*S* 16·5) than egg yolk $X_2$ (*S* 10). However, the sedimentation constants of Dr. Cook's purified lipovitellin and our egg yolk $X_2$ agree exactly (*S* 10), indicating that they may be identical substances. Also, our latest calculations of the sedimentation constants for the alkaline-produced sub-units of $X_2$ agree exactly (*S* 7) with those of Dr. Cook's sub-units of α- and β-lipovitellins. All molecular weights of the above substances, given in our papers, have been approximations and this has been so stated.

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# THE DISTRIBUTION OF ANTIGENIC GROUPINGS ON MOUSE GAMMA-GLOBULIN MOLECULES

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EDELMAN *et al.*[1] observed that certain antisera prepared in rabbits against human γ-globulin or human γ-myeloma proteins consistently gave two precipitation lines when tested by immunoelectrophoresis against normal human γ-globulin. When the antigenic properties of human γ-globulin fragments, obtained by digestion with papain and cysteine by the method of Porter[2], were examined by means of these antisera, the papain digests were found to contain fragments with two distinct antigenic groupings; these were referred to as 'fast' or *F* fragments and 'slow' or *S* fragments according to their relative rates of migration towards the anode during electrophoresis. Immunoelectrophoretic comparison of the original human γ-globulin with the papain digest indicated that the two precipitin lines given by human γ-globulin were due to antibodies against antigenic groupings shared exclusively with the *F* fragments and exclusively with the *S* fragments respectively. These findings are hard to explain if all molecules of undigested human γ-globulin have both *F*- and *S*-antigenic groupings on the same molecule, but would easily be accounted for if the *F*- and *S*-antigenic groupings were present on distinct γ-globulin molecules.

In the course of experiments on normal mouse γ-globulin and γ-myeloma globulins formed by transplantable plasma cell neoplasms, it was observed that rabbit antisera against normal mouse γ-globulin or the γ-myeloma protein formed by the plasma cell tumour line 5563 in $C_3H$ mice[3] could also give double precipitation lines with normal mouse γ-globulin on immunoelectrophoresis (Fig. 1). Mouse γ-globulin and myeloma protein, on treatment with papain and cysteine, have been found to form fragments with distinct antigenic groupings (*S* and *F* groupings)[4]. It was therefore possible to design an experiment to test directly whether *F*-antigenic groupings and *S*-antigenic groupings are present on distinct molecules in the undigested γ-globulin.

Normal mouse γ-globulin, prepared by zone electrophoresis on 'Geon 425' (British Geon Co.) by the method described by Fahey and Horbett[5], and 5563 myeloma protein purified by fractionation on

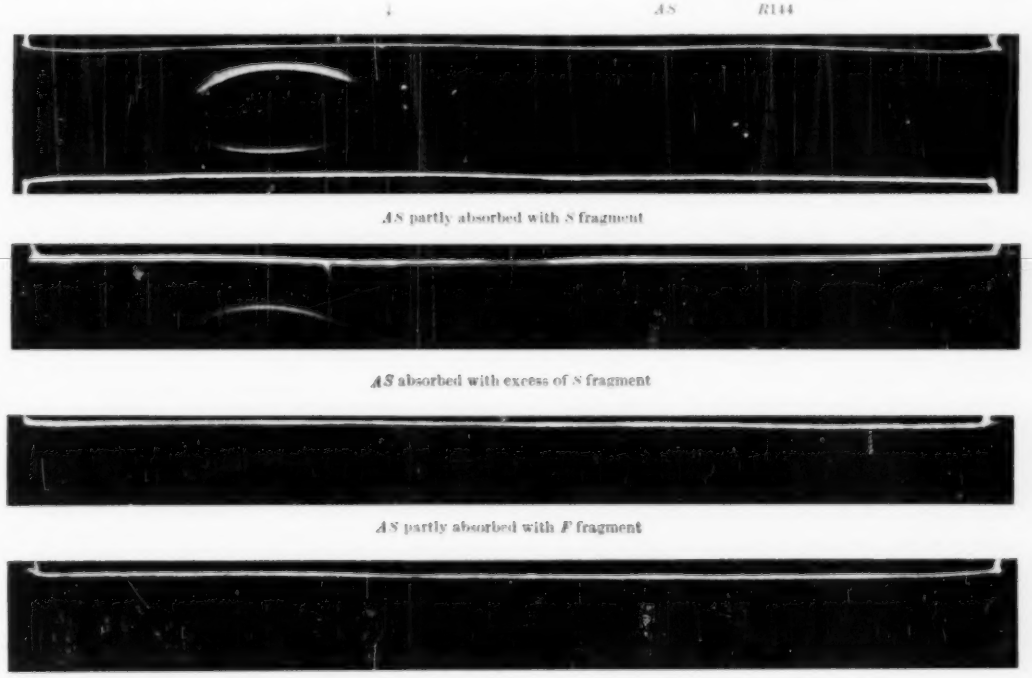
AS R144
AS partly absorbed with S fragment
AS absorbed with excess of S fragment
AS partly absorbed with F fragment
AS absorbed with excess of F fragment

Fig. 1. Double precipitin lines with normal mouse γ-globulin and absorbed antisera on immunoelectrophoresis. The arrow indicates point of application of purified normal mouse γ-globulin at a concentration of 5 mgm./ml. *AS R*144 rabbit antiserum against purified 5563 myeloma protein. This antiserum was absorbed with *S* and *F* fragments isolated from 5563 myeloma protein after treatment with papain and cysteine

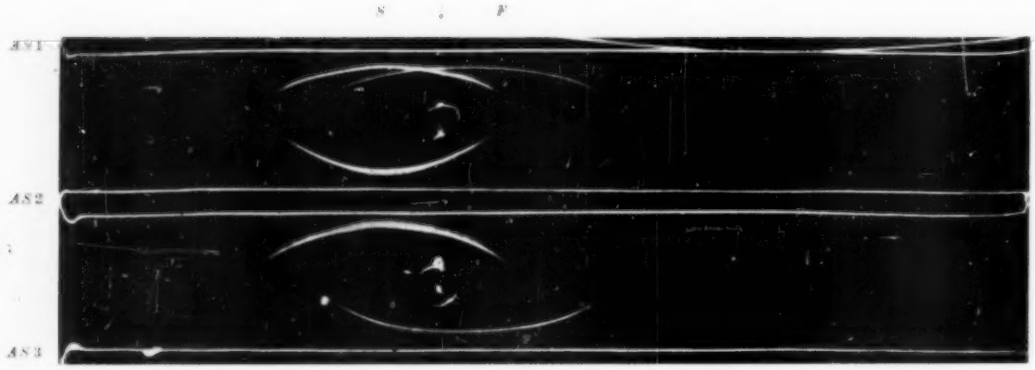


Fig. 2. Immunoelectrophoretic analysis of absorbed antisera. Arrow indicates point of application of papain and cysteine-treated 5563 myeloma protein. Fragments with distinct *S*- and *F*-antigenic groupings may be seen. *AS* 1, rabbit antiserum (*R* 91) again purified 5563 myeloma protein diluted by 1:2; *AS* 2, R 91 absorbed with a slight excess of fragment with *F*-antigenic grouping from papain and cysteine-treated 5563 myeloma protein.; *AS* 3, *R* 91 absorbed with fragment with *S*-antigenic grouping

DEAE cellulose[6] were labelled with iodine-131 at an average level of 0·5 atom/mole using the technique of McFarlane[7]. At least 99 per cent of the radioactivity was attached to protein having electrophoretic mobility characteristic of normal mouse γ-globulin and 5563 myeloma protein respectively. Samples of one rabbit antiserum prepared against normal mouse γ-globulin (*R*15) and of two antisera against 5563 myeloma protein (*R*144, *R*91) were absorbed with a slight excess of fragments (papain digest of 5563 myeloma protein) which had been purified so as to contain either *S*- or *F*-antigenic groupings only[4]. The absorbed antisera reacted exclusively with fragments possessing either *S*- or *F*-antigenic groupings, in contrast to the unabsorbed sera which reacted with both (Fig. 2).

Aliquots of the unabsorbed and of the absorbed antisera were mixed in a standard volume of saline with varying amounts of iodine-131 labelled normal mouse γ-globulin or iodine-131 labelled 5563 myeloma protein, giving ratios of antigen to antibody ranging from less to more than equivalence, and after 24 hr. at 2°, the proportion of iodine-131 labelled protein precipitated was estimated by centrifuging at 0°, and measuring the distribution of radioactivity between the supernatant and the antigen–antibody precipitate. The results (Table 1) showed that not only the unabsorbed antisera but also the absorbed antisera, specific for either *F*- and *S*-antigenic groupings, could precipitate 95 per cent or more of the normal mouse γ-globulin or 5563 myeloma protein labelled with iodine-131. Furthermore, by analysis of the precipitates at the equivalence points (Table 2), it was apparent that the total precipitable antibody was, within experimental error, equal to the sum of the antibody precipitable after each absorption, and there was no significant antigenic overlap between *S* and *F* fragments.

Table 1

| Rabbit antiserum | Absorbed with 5563 papain digest fragment | Per cent iodine-131 labelled protein precipitated in antibody excess: Normal mouse γ-globulin (iodine-131 labelled) | 5563 myeloma protein (iodine-131 labelled) |
|---|---|---|---|
| *R* 15 | — | 98·4 | 99·2 |
| *R* 15 | *S* | 98·3 | 99·2 |
| *R* 15 | *F* | 99* | 95·8 |
| *R* 91 | — | 98·9 | 99·5 |
| *R* 91 | *S* | 99* | 99·7 |
| *R* 91 | *F* | 99* | 99·1 |
| *R* 144 | — | 97·3 | 99·5 |
| *R* 144 | *S* | 92·6* | 99·5 |
| *R* 144 | *F* | 98·5* | 99·5 |

* Only 89–96 per cent of the iodine-131 labelled normal mouse γ-globulin was precipitated under the conditions described, but a further amount was co-precipitable with the rabbit antibody, on adding excess of goat antibody against rabbit γ-globulin. Iodine-131 labelled normal mouse γ-globulin in normal rabbit serum was not precipitated in these circumstances.

Table 2. Amount of γ-Globulin and Myeloma Protein Precipitated by Antisera reacting only with *S*- or *F*- Antigenic Groupings

| Antiserum | Mgm. antibody per ml. antiserum precipitated at equivalence by: normal mouse γ-globulin | | 5563 myeloma protein | |
|---|---|---|---|---|
| *R* 91 (anti-5563 myeloma protein) | 5·74 | | 6·9 | |
| *R* 91 absorbed with *S* fragment | 2·76 | 5·42 | 3·28 | 7·4 |
| *R* 91 absorbed with *F* fragment | 2·66 | | 4·12 | |

Our conclusion is that, in normal mouse γ-globulin as well as in the 5563 myeloma protein, the antigenic groupings of both the 'fast' and 'slow' papain digest fragments must be present on all the molecules. The double precipitin lines which we observed to occur between normal mouse γ-globulin and rabbit antisera cannot therefore be explained simply as due to a heterogeneous distribution of *F*- and *S*-antigenic groupings in the original normal mouse γ-globulin molecules. In fact we found (Fig. 1) that antisera partially or completely absorbed with *F* or *S* fragments still gave double lines with normal mouse γ-globulin on immunoelectrophoresis, although none of our antisera gave double lines with the 5563 myeloma protein. It is possible that an alternative explanation may lie in the presence in the antisera of antibodies with varying avidity for groupings the availability of which depends on the folding of the γ-globulin molecules, which is likely to be much more variable in normal mouse γ-globulin than in the more homogeneous myeloma protein.

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# FAVISM AND THALASSÆMIA IN SARDINIA AND THEIR RELATIONSHIP TO MALARIA

By M. SINISCALCO and L. BERNINI
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GLUCOSE-6-PHOSPHATE dehydrogenase deficiency of the red cell is a hereditary trait that predisposes to hæmolytic anæmia from *Vicia faba* beans, drugs (see review by Beutler[1]), and infections[2]. It has been suggested that this trait[3] and thalassæmia[4] have attained their world distribution by protecting their carriers against death from malaria. It would therefore be expected that populations exposed to severe and intense malarial infections in the historical past would have a high incidence of these traits — provided that the appropriate mutations had occurred or had been introduced into such populations. Inhabitants of the Sardinian plains, which until 1946 were among the most highly malarial areas in Europe[5], are known to have a high incidence of thalassæmia and favism. The island is even further suited for study because of the existence of isolated mountain villages where malaria is not prevalent.

Male school children of nineteen Sardinian villages that had in the past experienced varying incidences of malaria were studied. A dye decoloration test was used to detect glucose-6-phosphate dehydrogenase deficiency[6,7], and an osmotic fragility screening test and blood films served for the diagnosis of thalassæmia[8]. More detailed preliminary tests for thalassæmia, involving red cell enumeration, hæmoglobin, hæmatocrit, and hæmoglobin $A_2$ determination, and calculation of red-cell constants showed that the error of misclassification with the more rapid screening tests did not exceed 1 per cent[8]. The type of thalassæmia seen in one hundred randomly chosen families in different areas in Sardinia was associated with increased hæmoglobin $A_2$ levels[8,9].

Investigation of fifty-two families confirmed the fact that the enzyme deficiency is inherited as a sex-linked trait[10]. Linkage investigations in which colour-blindness was used as an *X*-chromosome marker showed no instance of recombination in 12 families among 4 large kindreds in which the two traits co-existed[10]. This finding formally rules out sex limitation or partial sex-linkage and indicates close linkage of the genes for colour-blindness and enzyme deficiency.

The data on the incidence of thalassæmia and enzyme deficiency are summarized in Table 1. Previous work on blood group distribution had indicated the similarity between populations in the central mountain villages (Desulo and Tonara) and east coast villages (Orosei and Galtelli)[6]. When this work was extended to west-coast villages (Terralba and Cabras), the low *Rh* (*cde*) and high blood group *M* gene frequencies characteristic of Sardinians were again found, suggesting that all population groups studied were ethnically homogeneous[11].

Fig. 1 demonstrates the positive correlation between thalassæmia and enzyme-deficiency gene frequencies, suggesting selection by a common ecological agent, namely, malaria by *Plasmodium falciparum*. It is apparent that the maximum gene frequency for thalassæmia (14 per cent) is significantly lower than that for enzyme deficiency (35 per cent). This finding is assumed to be related to the lethality of the thalassæmia gene in the homozygote state in contrast to milder selection against enzyme deficiency. It is also possible that the rate of accumulation of the thalassæmia gene is slower in populations with higher frequencies of enzyme deficiency, since this less harmful gene may already provide sufficient protection against malarial mortality.

Estimates of malarial morbidity were derived from the data of Fermi and Missiroli (see ref. 11 for literature), whose extensive investigations, carried out between 1929 and 1938, provide detailed information on the incidence of malaria in Sardinian villages. The relationship of the two genetic traits to the past incidence of malaria is shown in Fig. 2. There is good positive correlation between past malarial incidence and glucose-6-phosphate dehydrogenase deficiency

Table 1. ENZYME DEFICIENCY AND THALASSÆMIA IN SARDINIAN VILLAGES
(See also Bernini *et al.*, ref. 11)

| Village | Altitude (m.) | Malarial frequency (per cent)* | No. examined | Enzyme deficiency in males — gene frequency (±*S.E.*) | Thalassæmia — Heterozygote frequency | Thalassæmia — Gene frequency† (±*S.E.*) |
|---|---|---|---|---|---|---|
| Luras | 508 | 78 | 100 | 0·070 ± 0·025 | 0·225 | 0·112 ± 0·022 |
| Usini | 190 | 95 | 99 | 0·061 ± 0·024 | 0·142 | 0·071 ± 0·019 |
| Lodè | 345 | 90 | 163 | 0·294 ± 0·035 | 0·221 | 0·110 ± 0·017 |
| Siniscola | 42 | 55 | 198 | 0·113 ± 0·023 | 0·258 | 0·129 ± 0·024 |
| Benetutti | 406 | 50 | 100 | 0·090 ± 0·028 | 0·120 | 0·060 ± 0·017 |
| Suni | 333 | 85 | 98 | 0·143 ± 0·035 | 0·250 | 0·125 ± 0·023 |
| Orosei | 19 | 93 | 180 | 0·140 ± 0·026 | 0·188‡ | 0·094 ± 0·012‡ |
| Galtelli | 40 | 90 | 175 | 0·120 ± 0·024 | 0·213‡ | 0·106 ± 0·014‡ |
| Fonni | 1,000 | 10 | 100 | 0·030 ± 0·014 | — | — |
| Desulo | 891 | 33 | 313 | 0·031 ± 0·009 | 0·037‡ | 0·018 ± 0·005‡ |
| Tonara | 935 | 10 | 148 | 0·040 ± 0·016 | 0·047‡ | 0·023 ± 0·010‡ |
| Lanusei | 595 | 25 | 100 | 0·040 ± 0·019 | — | — |
| Tortoli | 15 | 90 | 50 | 0·160 ± 0·052 | — | — |
| Cabras | 9 | 97 | 200 | 0·350 ± 0·034 | 0·280 | 0·140 ± 0·024 |
| S. Giusta | 10 | 97 | 42 | 0·309 ± 0·075 | — | — |
| Terralba | 9 | 97 | 100 | 0·300 ± 0·046 | — | — |
| Isili | 523 | 17 | 100 | 0·090 ± 0·029 | 0·190 | 0·095 ± 0·021 |
| Gergei | 374 | 66 | 92 | 0·185 ± 0·040 | 0·131 | 0·065 ± 0·018 |
| Teulada | 50 | 90 | 101 | 0·169 ± 0·037 | 0·250 | 0·125 ± 0·023 |

* For refs. see Bernini *et al.*, ref. 11. † The gene frequency was calculated as one-half the heterozygote frequency because of lethality of homozygous thalassæmia. ‡ From Ceppellini, 1956 (includes both sexes).

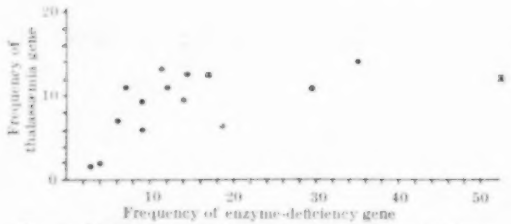


Fig. 1. Gene frequencies of thalassæmia and enzyme deficiency. Each dot represents one Sardinian village. The *X* refers to the data by Cohen *et al.* (ref. 15) on Kurdish Jews in Israel. (Note that the gene frequency of thalassæmia is approximately one-half the trait frequency, while the gene frequency of enzyme deficiency is identical with the trait frequency in males)

(or negative correlation with altitude; Table 1). To a lesser extent a similar correlation was observed for thalassæmia. Since the malarial frequency index refers to all malarial species, a still better correlation might have been obtained if the data could have been restricted to the lethal *P. falciparum* malaria. It is of interest that the sickling and the enzyme deficiency genes show a similar positive correlation in African populations[9]. There is extensive evidence now that sickle-cell heterozygotes are protected against death from *P. falciparum* malaria[12]. Data suggesting a similar protective effect on the part of the enzyme deficiency are now accumulating for African populations[3,7,13,14]. These results, as well as those presented here, therefore strongly implicate *P. falciparum* malaria as a selective agent for the maintenance of these red cell polymorphisms.

It was found that the presence of thalassæmia increased enzyme-levels, as measured quantitatively, in all genotypic classes, but especially in heterozygote females[8]. This increase probably was related to the presence of young blood cells, which are known to contain high enzyme-levels. Similar findings, based on the glutathione stability test, were obtained by Cohen *et al.*[15] in Kurdish Jews with the combined traits of thalassæmia and enzyme deficiency. Such an increase in enzyme-levels might be expected to decrease the frequency of clinical episodes of favism, and we investigated this possibility by surveying the medical records and carefully questioning 295 males and females more than fifty years of age in Lodé, where there was a frequency of enzyme deficiency of 29 per cent among males and a 22 per cent trait frequency of thalassæmia. No favism had occurred in individuals without enzyme deficiency. Of 50 subjects with both enzyme deficiency and thalassæmia, only 3 had had hæmolytic episodes, while among 121 with enzyme deficiency alone, 23 had had such episodes ($\chi^2 = 4{\cdot}6$, $P = < 0{\cdot}05 > 0{\cdot}02$ for 1 d.f.). It is therefore suggested that the presence of thalassæmia makes enzyme-deficient individuals less liable to acute hæmolysis from *V. fava* beans and probably also from infections and drugs. On the other hand, if malarial protection is related to low enzyme-levels[8], the presence of thalassæmia would partially deprive enzyme-deficient individuals of the malarial protection afforded by the enzyme deficiency while maintaining that given by thalassæmia. These considerations indicate the intricate interaction of two polymorphic red cell traits in a population. It is likely that full understanding of the population dynamics of these and many other human genes will require further detailed investigation of interactions of this type.

Fig. 2. Present gene frequency of enzyme deficiency (○) and thalassæmia (●) against malarial prevalence before eradication of malaria in Sardinia. Each dot represents a village. Not all villages were screened for both traits

These investigations were supported by grants of the Rockefeller Foundation, the Italian National Research Council, and Grant *H*-3091 of the U.S. National Institutes of Health.

*Note added in proof.* The very close linkage between the genes for enzyme deficiency and colour-blindness is supported by additional observations made during the past nine months or so by us in Sardinia. From these it has become clear also that the incidence of colour-blindness itself is positively correlated with the past incidence of malaria and therefore with the frequency of the enzyme deficiency. The situation is interpreted as an example of the selection of a neutral gene through the close linkage with a highly adaptive one. The hypothesis is further strengthened by the finding of an excess of families of the coupling type in the isolated village so far studied with almost complete ascertainment (Lodé), as would be expected if the fittest genotype versus malaria were represented by the enzyme-deficient male.

The recent results of Adam (*Nature*, **189**, 686; 1961) confirm the close linkage between the two genes in Israel but show an excess of families of the repulsion type. It would be interesting to know in this connexion: (i) whether or not this was due to ascertainment; (ii) if all the families reported were derived from a single breeding unit and if this is of recent formation; (iii) if the propositi are the sons of people coming from different populations where the frequencies of the two genes were fixed at different equilibrium-levels.

Further discussion on these problems and the additional results from Sardinia will be reported in detail elsewhere.


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*by* **R. E. MARSHAK** *and* **E. C. G. SUDARSHAN,** *Department of Physics & Astronomy, University of Rochester*

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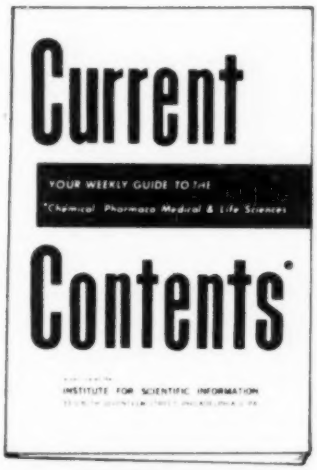


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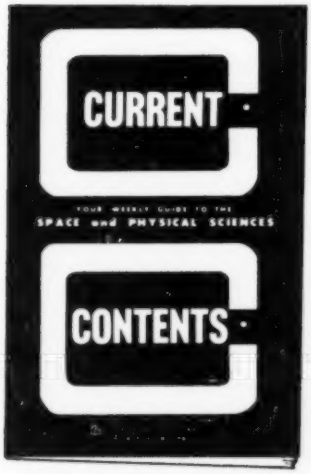


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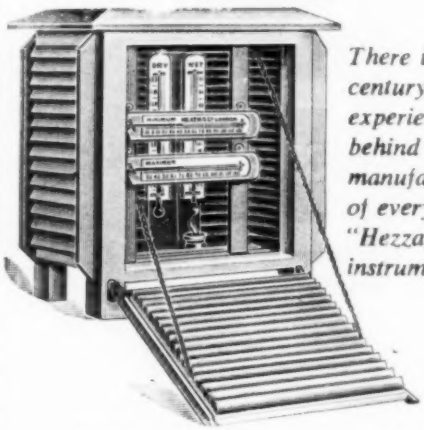

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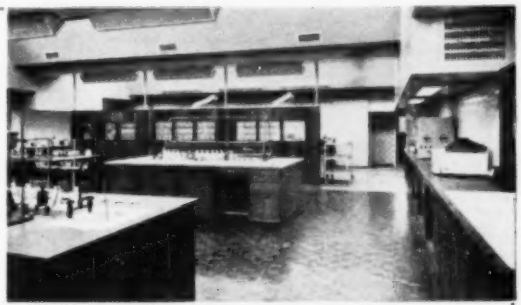

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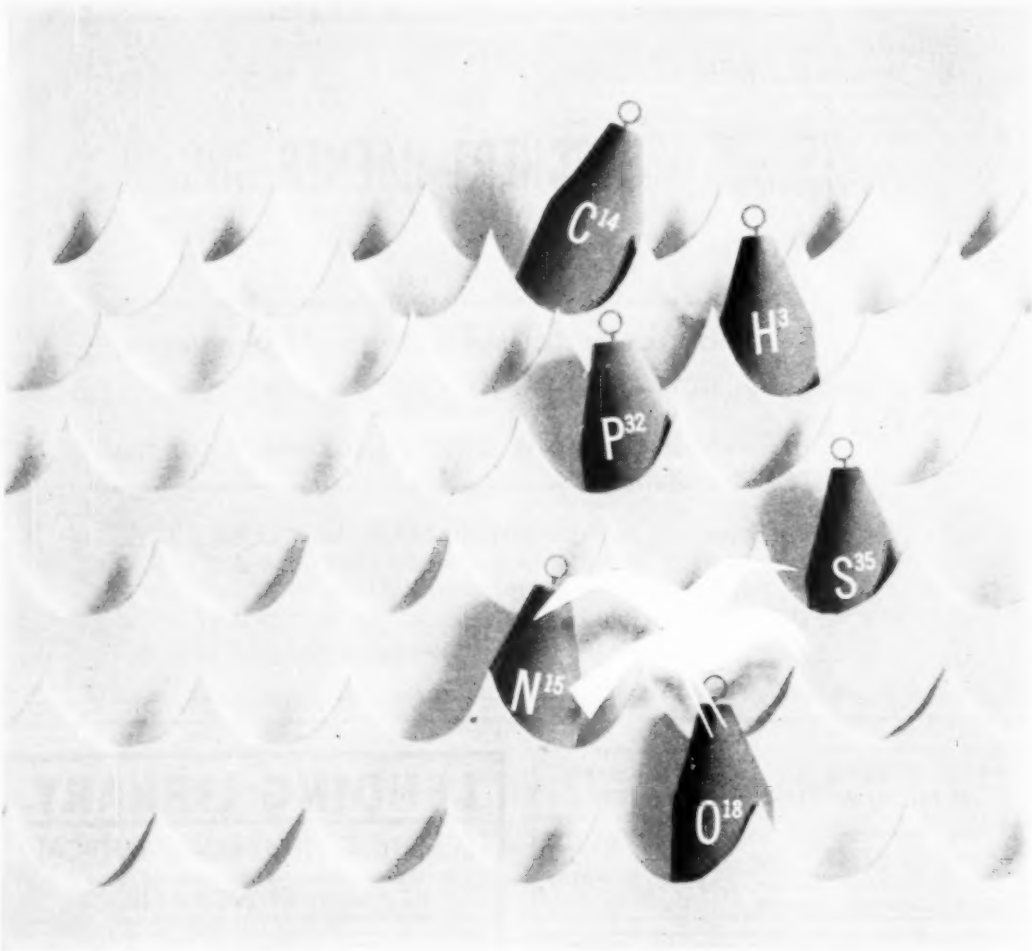


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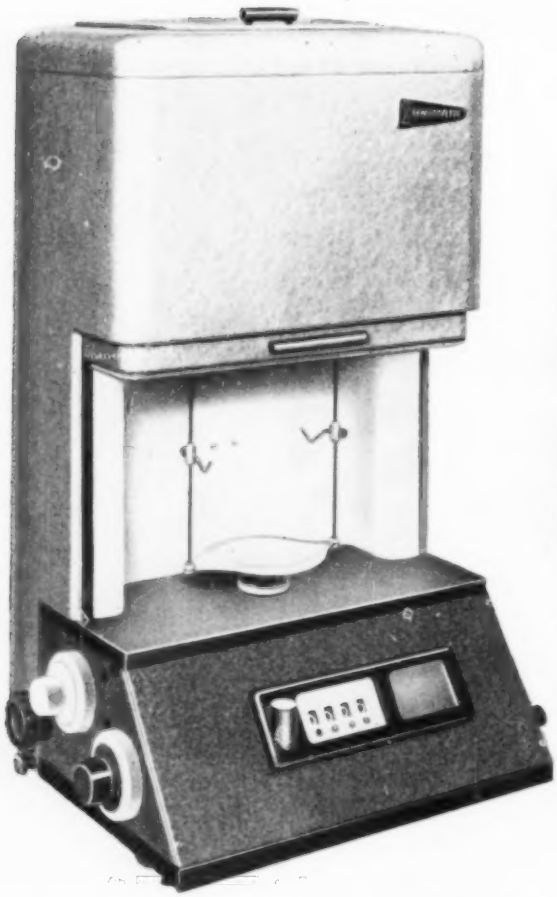

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# LETTERS TO THE EDITORS

## PHYSICS

### Coesite as an Inclusion in G.E.C. Synthetic Diamonds

In the course of X-ray diffraction work on synthetic diamonds[1], many specimens were found to contain polycrystalline inclusions. A sample of coesite[2] made at the National Physical Laboratory, and kindly given to us by Sir Gordon Sutherland, has enabled us to identify it as the most prominent of the inclusions encountered (see, for example, ref. 1, Plate X, Figs. 1, 2).

This result is of interest for two reasons. In the first place, coesite has recently been identified in the Meteor Crater in Arizona[3], where its presence is taken as evidence of the occurrence of an impact shock-wave of sufficient intensity to result in the production of crypto-crystalline diamond[4], a possibility which has actually been demonstrated by de Carli and Jamieson[5]. One specimen in which coesite was found was actually the first synthetic diamond we ever examined, being a group of parallel black cubes which was selected from a batch in the G.E.C. Laboratories in Schenectady because of its superficial resemblance to cliftonite, the cubic graphite found in meteorites[6]. However, no graphite was detected in this specimen.

The second reason is that geologists have long suspected that reported inclusions of quartz in natural diamond were in reality *intrusions*, as quartz could scarcely be expected under the conditions likely to prevail during the genesis of diamond[7]. The identification of coesite strongly supports this point of view, since it indicates that if crystalline $SiO_2$ were present at all, it would almost certainly have been the high-pressure form. Some X-ray photographs of natural diamonds indicate the possible presence of coesite. A search for further specimens is in progress. If substantiated, this would represent the first natural occurrence of coesite except in meteor craters.

H. Judith Milledge

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University College,
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### Thermal Diffusion of Oxygen and Nitrogen in Zirconium

The diffusion of oxygen in zirconium under the influence of an electric field has already been studied qualitatively[1]. Before beginning a further investigation of this phenomenon, it seemed worth while to find out whether a diffusion of the 'Ludwig Soret-type' occurred. If, under the influence of a temperature gradient, oxygen were indeed to diffuse preferentially in the direction of increasing or decreasing temperature, such an effect would be superimposed on the diffusion under the influence of an electric field if resistance heating were applied on the zirconium wire or sheet. The reason for this is that when the oxygen moves to the anode, the concentration of oxygen in that region rises, the electrical resistance increases locally and thus a temperature gradient develops along the wire or sheet. Darken and Oriani[2] have found a thermal diffusion of carbon and nitrogen in iron under the influence of a temperature gradient. They could show that both nitrogen and carbon diffuse to the region of the highest temperature. In order to evaluate such an effect in the case of oxygen in zirconium, we tried several experimental methods. The most reproducible results were obtained in the following circumstances.

As the hardness of zirconium and of tantalum is very sensitive to small amounts of oxygen (or nitrogen)[3], we used measurements of the hardness to determine the oxygen content. We carried out our experiments with ribbons of zirconium (free of hafnium, brand I.C.I. and Hereaus) first 140$\mu$ thick and 6 mm. broad, later 200$\mu$ thick, 6 mm. broad and in both cases 70 mm. long. An amount of oxygen was measured by volume and pressure and then absorbed in the zirconium by subjecting the strip to resistance heating (a.c.) at about 1,200° C. The solution was homogenized by subsequent heating at 1,350° C. during 4 hr. in a high vacuum. At various sites on the strip the homogeneity was checked with hardness measurements.

It proved very difficult to operate a furnace (to obtain a temperature gradient) in a vacuum of about $10^{-5}$ mm. mercury, without producing contaminating gases. Zirconium readily absorbs these gases. Therefore, resistance-heating (with a.c.) was applied in the experiments on thermal diffusion. The temperature gradient was realized by cutting away part of the ribbon so as to decrease its width towards one end, or so that the width diminished from both ends towards the centre (Fig. 1). In cases where the sheet was too brittle (more than 5 atm. per cent oxygen) to be cut, part of the material in the middle was etched away. After the gradient heating, several micro-hardness tests were made on each of a number of distances from one of the ends of the ribbon. Good reproducibility was obtained in the tests at constant distance from the end.

It was found that the oxygen moves in the direction of the lower temperature. Strips of zirconium with 1 and 2 at. per cent oxygen subjected to heating with a temperature gradient of 1,100–1,700° C. over a length of 50 mm. gave a decrease of the hardness (or oxygen content) on the site which had been at

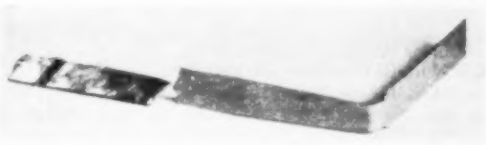

Fig. 1. Strip of zirconium with 6 at. per cent oxygen, after gradient-heating. The thinnest part is ductile and bent, the thick parts remain brittle and one end is broken

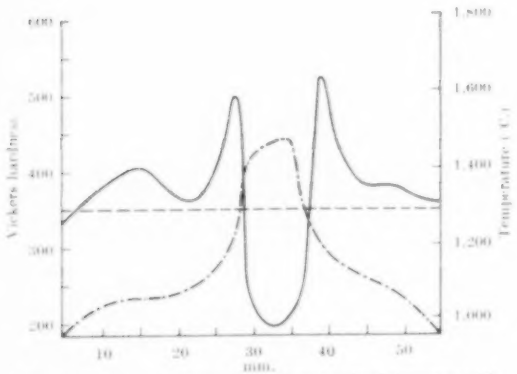


Fig. 2. Hardness and temperature along a strip of zirconium with (initial) 6 at. per cent oxygen. Annealing for 20 hr. at 1,000–1,460° C. ——, Hardness before annealing; ———, hardness after gradient annealing during 20 hr.; — · —, temperature along the strip during annealing

the highest temperature, and a rise in hardness (oxygen content) in the region which had been at a lower temperature. The same phenomenon occurred in strips with an oxygen content of 4 at. per cent after gradient-heating 1,350–1,700° C. In all these cases every part of the strips could be assumed to be in the region of the β-phase, according to the phase diagram of zirconium oxygen as given in ref. 4. Strips with 4 at. per cent oxygen or more, heated for 20 hr. with a gradient 900–1,450° C., had (according to the same phase-diagram) their high-temperature parts in the β-region. The low-temperature part would be in the α-region, therefore the different solubilities of oxygen in the α- and in the β-phase (more oxygen will dissolve in the α-phase of zirconium) would have a part to play. This difference in solubility of the oxygen in α- and β-zirconium might enhance the movement of the oxygen away from the high-temperature part.

In some experiments the diffusion reduced the oxygen content of the high-temperature part almost to zero and, as a result, this part became as ductile as pure zirconium, whereas the other parts remained brittle. The phenomenon is demonstrated in Fig. 1, Fig. 2 giving the plot of hardness and temperature along the length of the strip. A strip of zirconium not loaded with oxygen, but subjected to the same gradient heating, showed scarcely any difference in hardness along its length.

There are indications that nitrogen in zirconium and oxygen in titanium behave in the same way as oxygen in zirconium.

We conclude, therefore, that when oxygen or nitrogen is dissolved in zirconium a 'Ludwig Soret-effect' occurs, which causes the oxygen or nitrogen to move to that part of the metal which has the lower temperature. We shall report more extensively on these experiments and also try to determine this diffusion effect quantitatively.

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## Elastohydrodynamic Lubrication of Rollers

It is now well known that the lubrication at such nominal line contacts as are found in roller races and between gear teeth is hydrodynamic in character. It is also known that this lubrication possesses peculiar features not found in journal bearings and which arise from the high pressure—a pressure, for example, of tens of tons per square inch as compared with 100 lb. in.$^{-2}$. Because of the pressure the surfaces are deformed, in general elastically, and in addition within the pressure zone the oil acquires a much higher viscosity than it normally possesses; the viscosity might be greater by a thousand-fold. These circumstances have excited much inquiry as to the shape in cross-section of the hydrodynamic film. This communication reports an experimental measurement of that shape.

The measurements have been made with 3-in. diameter disks, one of which was of glass and which rolled with other disks of hardened steel. All were polished. The glass disk carried the evaporated chromium electrode shown in plan in Fig. 1*a* and electrical connexions were made as shown in Fig. 1*b*. As the leading edge of the electrode approaches and passes through the conjunction of the surfaces the capacitance formed by the electrode and the steel disk rises, and it may be shown that to a sufficient accuracy the potential appearing across the resistor is proportional to $\varepsilon/h$, where $h$ is the gap separating the disks at the leading edge and $\varepsilon$ is the dielectric constant of the intervening medium. Results have been obtained up to loads of 600 lb. per in. of face-width and peripheral speeds of 30 ft. per sec.

A typical result is shown in Fig. 2. This is an oscillograph showing the potential across the resistor as a function of time and will be treated as a plot of $\varepsilon/h$ against distance. The film has a parallel section which, in the example shown, was found to be 1μ in thickness in agreement with previous measurements

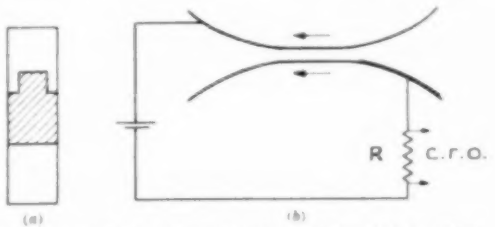


Fig. 1. *a*, Plan of chromium electrode; *b*, electrical connexions

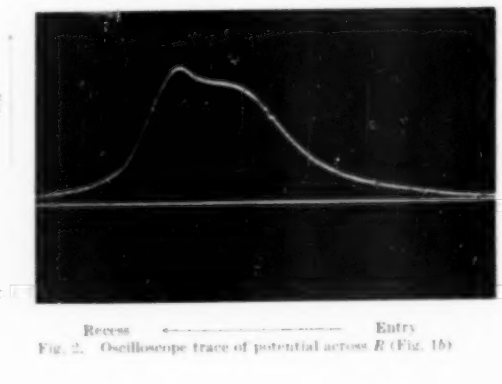


Fig. 2. Oscilloscope trace of potential across $R$ (Fig. 1*b*)

by another method[1]. Another notable feature of the figure is that the parallel section is followed by a constriction in which the film thickness falls by approximately 10 per cent. These features confirm qualitatively theoretical ideas propounded in an approximate analysis by Grubin[2] and recently by Dowson and Higginson[3] and Archard, Gair and Hirst[4] in more exact analyses. The parallel section confirms that the pressure distribution is approximately Hertzian, while the constriction implies that somewhere towards the recess edge the pressure exceeds that of the Hertzian distribution. The practical implication of the excess pressure is that the material of the disks might be more severely stressed than is suggested by the Hertzian analysis on which design is at present based. The practical implication of the constriction is that it is the most probable site for breakdown of the oil film and the initiation of surface damage. A fuller account of the results will be published later.

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## Phase-Velocity of Ultra-sound in the Primary Aliphatic Amines

Continuous-wave electronic measurements of the speed of sound in liquids commonly depend on the presence of appreciable standing-waves in paths of low absorption, the half-wave-length being determined by detection of successive resonances as the path-length[1] or frequency[2] is changed. Alternatively, for liquids of high absorption in which the energy content of the standing-wave is necessarily small, the wave-length may be found by direct comparison of the phases of the transmitted and received signals. In conditions of very high absorption it has been necessary to use pulse techniques to obtain adequate acoustic intensity at the receiving transducer consistent with tolerable energy dissipation in the medium.

I have devised an alternative method of measurement employing continuous-wave frequency-modulated ultra-sound. The lower permissible signal noise ratio in a frequency-modulation system allows operation at much-reduced acoustic intensities. The path occupied by a complete period of the modulation in a liquid sample is determined. The liquid is contained in an interferometer having separate transmitting and receiving quartz transducers. The frequency of the ultra-sound is varied sinusoidally by approximately ±40 kc./sec. about a mean of 10·7 Mc./sec. The modulation of the received ultra-sound is detected by a ratio discriminator preceded by a limiting stage. The observed absence of distortion of the detected modulation indicates that any dispersive effect in the liquids tested is too small to have appreciable effect for the frequency deviation used. Phase-lag of the received modulation is measured by inversion and linear addition to a sample of the transmitted modulation of equal amplitude. In the absence of phase-shift of electronic origin, the resultant is zero when the time of transit is an integral number of periods of the modulation, a condition obtained by adjustment of the modulating frequency. The phase-velocity is then given by:

$$v = Lf/N$$

where $L$ is the length of the column, $f$ is the modulating frequency and $N$ is an integer. A range of path-lengths is used as a check on diffraction effects, and $N$-values are varied up to 4 as a check on consistency of behaviour of the electronic equipment. The temperature of the liquid is stabilized at 19·3 ± 0·1° C.

The first application of the method has been to the homologous series of primary aliphatic amines. Measured phase-velocities ($v$) appear in Table 1, the uncertainties being about 3 m.sec.$^{-1}$.

Table 1

| Liquid | $v$ (m.sec.$^{-1}$) | $R$ $\left(\frac{\text{cm.}^3}{\text{mole}}\left(\frac{\text{m.}}{\text{sec.}}\right)^{1/3}\right)$ | $\Delta R$ $\left(\frac{\text{cm.}^3}{\text{mole}}\left(\frac{\text{m.}}{\text{sec.}}\right)^{1/3}\right)$ |
|---|---|---|---|
| *n*-Propylamine | 1,234 | 877 | |
| | | | 194 |
| *n*-Butylamine | 1,269 | 1,071 | |
| | | | 187 |
| *n*-Amylamine | 1,296 | 1,258 | |
| | | | 186 |
| *n*-Hexylamine | 1,317 | 1,444 | |
| | | | 189 |
| *n*-Heptylamine | 1,345 | 1,633 | |
| | | | 191 |
| *n*-Octylamine | 1,354 | 1,826 | |
| | | | 198 |
| *n*-Nonylamine | 1,372 | 2,024 | |

Values of the molecular velocity defined in ref. 3 as:

$$R = v^{1/3} M/\rho$$

appear in the second column, $M$ being the molecular weight and $\rho$ the density. The increments $\Delta R$ with addition of successive —$CH_2$— groups are tabulated in the third column. It is evident these are approximately constant, the mean being 190.

The constancy of $\Delta R$ was demonstrated by Rao[4] for six homologous series, an overall average of 195 being obtained. Weissler[1] obtains 190 for series of alcohols including branched isomers and ring molecules. More recently, Leon[5] quotes Mikhailov and Nizhin (1947) as obtaining 189 for the *l*-olefines, and gives an average of 188 for some higher paraffins.

It is hoped to publish a detailed account of the research elsewhere.

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# METALLURGY

## Effect of a Thin Oxide Film on the Reaction of Iodine Vapour with Copper

In experimental work on the oxidation of metals the preparation of specimens is directed to the removal of contaminants such as grease, the production of a consistently smooth or rough surface and the realization of a stable metallurgical structure defined by the grain size and texture. The congenital

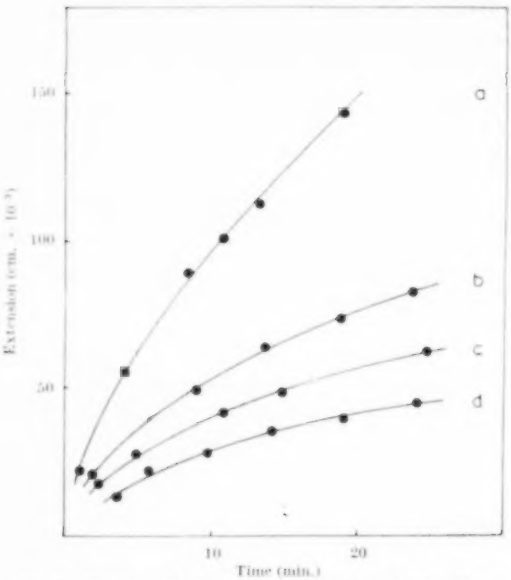


Fig. 1. Reaction of iodine vapour with copper at 285 ± 1° C., iodine reservoir at 16 ± 0·2° C. Times of room temperature exposure of specimens to the atmosphere before reaction : *a*, about 10 min.; *b*, 1 day; *c*, 3 days; *d*, 8 days

thin oxide film, which may increase in thickness on abrasion and polishing, or change in identity on electrolytic treatment, or disperse on heat-treatment *in vacuo*, is recognized as influencing the extent of the subsequent oxidation, but is largely ignored in discussions of the oxidation mechanism. In cases where the gaseous reactant is not oxygen, the thin oxide film, having no identity with the reaction system, assumes a different significance. Intuitively this is thought of in terms of protection and some results obtained in a preliminary study of the reaction between copper and iodine vapour demonstrate this.

Specimens (1 × 3 cm.) were cut from the centre of a 6-in. wide strip of 0·004-in. thick cold-rolled copper, de-greased with acetone and heated in an evacuated glass capsule at 500° C. for 1 hr. After cooling and opening the capsule the specimens were stored in a desiccator until required. The reaction was followed gravimetrically using a calibrated 'Pyrex' glass spring of sensitivity 17·37 cm.gm.$^{-1}$, and a cathetometer which could be read to 0·001 cm. The specimen was suspended from the spring by a thin silica rod which carried a fiduciary mark, and this assembly was further suspended in a vertical glass reaction tube, the lower closed end of which served as the iodine reservoir. The reaction zone was provided by a tube furnace, its temperature being controlled with a conventional circuit incorporating an auto transformer and 'Electroflo' controller. Temperature measurement was carried out potentiometrically, using a calibrated platinum – 13 per cent rhodium couple placed in a well extending into the reaction zone and sealed into the reaction tube.

With an acetone–solid carbon dioxide bath surrounding the iodine reservoir and a specimen in position, the apparatus was evacuated ($10^{-3}$ mm. mercury) while the reaction zone was heated. When the steady controlled temperature was achieved, the reaction tube was isolated from the pump, the cold bath replaced by a water jacket, and readings of the cathetometer were made at suitable intervals.

The reactions were carried out at 284 ± 1° C. with the iodine reservoir at 14 ± 0·2° C. The results of these measurements are shown in Fig. 1, where the extension of the spring is plotted as a function of time, and each specimen is identified by the time of its exposure to the atmosphere between its removal from the heat treatment capsule and its suspension in the reaction tube.

It is seen that the increase in this time of exposure results in a retardation of the formation of cuprous iodide, which is due apparently to the presence of an oxide film of increasing thickness. This explanation requires the disappearance of the original oxide film during the vacuum heat-treatment at 500° C. in favour of a solution of oxygen in copper, with the internal precipitation of oxide at concentrations above the solubility limit; the continuous growth of a new oxide film at room temperature over these times of exposure to the atmosphere; and the diffusion processes above to take place at such a low rate at the reaction temperature that the new oxide film remains intact. This leads to a picture of the reaction in which the oxide film is conferring some protection on the copper, and from which it may be inferred that in the absence of such a film, as would obtain with hydrogen reduction of the specimen within the apparatus, the reaction would be very fast.

It would appear further that transport through the oxide film is largely determining the rate of reaction, superimposed on the characteristic diffusion kinetics in the growing iodide film. In view of the lack of knowledge of the thickness of the oxide films and the inherent uncertainty in this experiment of establishing precisely the time of commencement of the reaction, an analysis of these measurements has not been made. A more detailed study is, however, now in progress.

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## GEOLOGY

### Determination of the Age of a Basic Igneous Intrusion by the Potassium–Argon Method

Potassium–argon age determinations have been carried out mainly on minerals with a high potassium content, particularly micas and potassium feldspars, found in intermediate to acid igneous rocks, but little work has been done on minerals with a low content of potassium, such as occur in basic igneous rocks. However, Hart *et al.*[1] have shown recently that it is possible to obtain reliable ages using hornblende and pyroxene. I decided to investigate the relative argon retention properties of pyroxene, plagioclase and sanidine in two specimens from a Tasmanian dolerite body, and in so doing hoped to determine the time of intrusion of the dolerite. The presence of chilled margins to these dolerite intrusions also suggested the possibility of carrying out potassium–argon dating on a whole rock sample from such a contact.

Table 1. Potassium–Argon Age Measurements on Tasmanian Dolerites

| Sample No. | Specimen No. | Mineral | Potassium analyses (per cent) | Average potassium (per cent) | Diff. in potassium (per cent) | $^{40}Ar/^{40}K$ | Air correction (per cent) | Calculated age (m.y.) |
|---|---|---|---|---|---|---|---|---|
| *KA* 811 | *M*205 | Sanidine | 7·10, 7·05 | 7·075 | 0·7 | 0·008692 | 23·4 | 143·2 |
| *KA* 811*R* | *M*205 | Sanidine | 7·10, 7·05 | 7·075 | 0·7 | 0·008771 | 14·2 | 144·5 |
| *KA* 833 | *M*207 | Sanidine | 6·76, 6·66 | 6·71 | 1·5 | 0·009569 | 17·2 | 157·0 |
| *KA* 833*R* | *M*207 | Sanidine | 6·76, 6·66 | 6·71 | 1·5 | 0·009508 | 19·6 | 156·1 |
| *KA* 812 | *M*205 | Plagioclase | 0·568, 0·578 | 0·573 | 1·7 | 0·010181 | 18·1 | 166·7 |
| *KA* 812*R* | *M*205 | Plagioclase | 0·568, 0·578 | 0·573 | 1·7 | 0·010239 | 25·6 | 167·6 |
| *KA* 834 | *M*207 | Plagioclase | 0·525, 0·519 | 0·522 | 1·1 | 0·009574 | 56·4 | 160·3 |
| *KA* 834*R* | *M*207 | Plagioclase | 0·525, 0·519 | 0·522 | 1·1 | 0·009680 | 19·1 | 158·8 |
| *KA* 813 | *M*205 | Pyroxene | 0·245, 0·237 | 0·241 | 3·3 | 0·009881 | 22·9 | 162·0 |
| *KA* 835 | *M*207 | Pyroxene | 0·171, 0·169 | 0·170 | 1·2 | 0·01017 | 28·4 | 166·5 |
| *KA* 810 | *M*172 | Chilled dolerite | 0·747, 0·750 | 0·7485 | 0·4 | 0·009007 | 40·6 | 148·2 |

$\lambda = 5{\cdot}304 \times 10^{-10}$ yr.$^{-1}$ $\quad \lambda_e = 0{\cdot}584 \times 10^{-10}$ yr.$^{-1}$

The Tasmanian dolerites, which are tholeiitic in composition[2], were intruded into an essentially flat-lying sequence of Permian and Triassic sediments approximately 4,000 ft. in thickness, as sheets up to 2,000 ft. thick, as large transgressive bodies and as dyke-like intrusions which exceptionally may be one mile in width. The dolerite crops out over an area exceeding 6,000 square miles, mainly in the eastern half of Tasmania. The youngest sediments which the dolerite intrudes are considered to be Middle or possibly Upper Triassic in age[2], on the basis of the plant fossils present, so that the dolerite is younger than this. Lower Tertiary fresh-water sediments occur overlying dolerite in northern Tasmania[3], placing an upper limit on the age of the dolerite. By analogy with the Karroo dolerites, which are Liassic to Lower Cretaceous in age[4,5], and which are quite similar in composition to the Tasmanian dolerites, a Jurassic age has generally been assigned to them. Analyses of the chilled dolerites from the contacts of the intrusions are all closely similar[2], suggesting that the Tasmanian dolerite magma was intruded over a relatively short period of time.

Two specimens of fayalite granophyre and a chilled contact dolerite from the large Red Hill Dyke, 20 miles south-west of Hobart in southern Tasmania, were chosen for the age determinations. The fayalite granophyre is a differentiate of the dolerite magma and consists essentially of plagioclase ($anorthite_{40}$) comprising 48 per cent by volume, pyroxene—a ferroaugite (8 per cent), fayalite (4 per cent), potassium feldspar (16 per cent), quartz (19 per cent) and iron ore (2 per cent). The potassium feldspar, which has a composition about $orthoclase_{80}$, belongs to the sanidine-anorthoclase cryptoperthite series of Tuttle[6], and by the definition of MacKenzie and Smith[7] it is a sanidine from its optical properties. The chilled dolerite is composed of microphenocrysts of plagioclase, orthopyroxene and clinopyroxene amounting to about 7 per cent of the rock, set in a microcrypto-crystalline ground-mass which has the appearance of devitrified glass.

The fayalite granophyres were crushed to −60 +100 mesh, and plagioclase, pyroxene and sanidine were separated using bromoform. The separated minerals were split into two portions, one of which was used for duplicate potassium analyses and the other for the argon extraction. In some cases duplicate argon runs were made. The argon extraction on the chilled dolerite was run on a single uncrushed piece of the rock and the potassium on a sample crushed to −100 mesh.

The potassium analyses were made by using a Perkin-Elmer flame spectrophotometer with lithium as an internal standard. The $R_2O_3$ group and lime were removed by precipitation before the potassium was determined. The argon extractions were carried out in a high-vacuum line originally at a pressure of about $10^{-8}$ mm. mercury, and the sample was fused by induction heating. A tracer of argon-38 was added to the evolved gases, which were cleaned up by reaction in copper oxide and calcium furnaces. The isotopic composition of the purified argon was determined by means of a Reynolds-type mass spectrometer[8].

The results are set out in Table 1. The agreement between duplicate potassium analyses is in all cases better than 2 per cent of the amount present, except for pyroxene *KA* 813. The low concentration of potassium in the pyroxenes makes it difficult to attain high precision in the analysis. The rock was only crushed to −60 +100 mesh in order that losses of argon due to grinding would be negligible, so that some composite grains were present in the pyroxene concentrates, which could not be removed by the usual methods of purification. In both pyroxenes the impurities, which consisted mainly of plagioclase with minor sanidine, accounted for less than 5 per cent of the sample. However, because of the relatively high potassium content of the impurities, compared with the pyroxene, about half of the potassium in *KA* 813 and approximately one-third of the potassium in *KA* 835 is attributable to the impurities. The plagioclase separates were better than 98 per cent pure and those of sanidine contained approximately 5 per cent impurity of altered plagioclase.

The calculated ages range from 143 to 168 million years, but the plagioclase and pyroxene results gave ages ranging from 159 to 168 million years, a spread of less than 6 per cent. As these two minerals have quite dissimilar crystal structures this small spread of calculated ages suggests that argon retention, in both minerals, is high. Therefore it is considered that the calculated age approaches the true age closely, and that the time of intrusion of the Tasmanian dolerites was near 167 million years ago, the higher figure being preferred, as any loss of argon which may have occurred would lower the age. This corresponds to an age approximately at the boundary of the Lower and Middle Jurassic[9,10]. Although difficult to place probable errors on the physical measurements, replicate argon determinations, in all cases, agree to within 1 per cent, indicating a very high precision. The reproducibility of the potassium analyses is generally less than that in the argon measurements, showing that greater attention must be paid to refining the techniques for the determination of potassium.

The calculated ages for the sanidines are somewhat lower than those for plagioclase and pyroxene, suggesting some leakage of argon. The very low calculated age for sanidine *KA* 811 as compared with *KA* 833 is surprising, as both minerals appear to be

very similar in thin section. They both appear to be homogeneous, as no unmixing has been observed, although it may be present on a sub-microscopic scale. The sanidines are slightly turbid as a result of deuteric alteration, and this has probably aided leakage of argon. A satisfactory explanation for the loss of argon from potassium feldspars and, in particular, loss from the high temperature, homogeneous, monoclinic sanidines has not yet been advanced; a thorough structural study of this group of minerals in conjunction with their observed argon retention properties is urgently required. It may be noted, however, that some sanidines, and particularly those with a high potassium content, do retain argon quantitatively (ref. 11 and Evernden, J. F., personal communication).

The single chilled dolerite result gives 148 million years, which is a surprisingly good age considering that the rock is composed mainly of devitrified glass, and hence might be expected to lose considerable argon.

In conclusion it may be stated that the Tasmanian dolerites were intruded some 167 million years ago at approximately the boundary of the Lower and Middle Jurassic, and that it has been demonstrated that minerals with a low potassium content, such as occur in basic igneous rocks, can be used for age determinations by the potassium-argon method. Chilled dolerites and possibly glassy basalts will also give some aid in the elucidation of the age of basic igneous rocks by this method.

Grateful acknowledgment is made to Dr. G. H. Curtis and Dr. J. F. Evernden for the use of their facilities and to them and Mr. J. Obradovich for their interest and help in this work. This work was carried out while I held a Commonwealth Scientific and Industrial Research Organization (Australia) post-graduate overseas studentship, for which thanks are expressed.

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## Erosion Surfaces in the Caribbean and their Significance

Altimetric analysis of a series of topographic maps covering the main Cordillera of Puerto Rico indicates the existence of erosion surfaces, represented largely by concordant summit-levels, at the following average elevations: 760, 620, 470, 330 and 160 m. above present sea-level[1]. Field work at present in progress suggests that these elevations in fact represent mean elevations of groups of stepped surfaces, in some instances bearing sedimentary deposits which have been described previously as residual soils.

At the present time it is not possible to reach any firm conclusion as to the mode of origin of these surfaces; but their distribution, at least in western Puerto Rico, suggests that they probably originated as marine cut surfaces, later modified by sub-aerial processes as they successively emerged from the sea. Whatever conclusion is eventually reached as to their origin, it seems fairly certain that they are related to changing sea-levels, the more widespread surfaces—particularly the 330 and 160 m.—presumably representing periods of relative standstill.

Examination of these surfaces was originally undertaken in the hope of determining the tectonic movements that had affected the island subsequent to middle Miocene times. However, Choubert[2] has described a series of surfaces in French Guiana with the following mean elevations: 600 (+), 500, 330, 235 and 160 m. These show a remarkable parallelism with the Puerto Rican levels, and this is borne out when the ranges of elevation of each surface are taken into account. In Puerto Rico, the 330- and 160-m. groups of surfaces are perhaps the most conspicuously developed and, from Choubert's map, this seems to be the case in French Guiana, too.

Furthermore, Martin-Kaye[3] has directed attention to the conspicuous concordance of summits in the northern Lesser Antilles at, or just above, 1,000 ft. This would seem to correlate with the 330-m. group in Puerto Rico and French Guiana. It seems scarcely likely that such correspondence of levels is a chance one, and I was reluctantly forced to the conclusion that these levels must be related to large eustatic lowering of sea-level and that the stage-by-stage emergence of Puerto Rico was not brought about by tectonic movements as had previously been taken for granted. An overall fall in sea-level since pre-glacial times has already been postulated by Wooldridge[4] and others, at least from 600 ft. above present sea-level, and even greater movements of sea-level have been hinted by Baulig[5] and Hollingworth[6].

The obvious difficulty in the way of accepting such large eustatic lowering of sea-level lies in the mechanism which would dispose of such large quantities of water. Geyl[7] has postulated a mechanism involving continental 'shift' induced by deep convection currents and isostatic readjustment of the continental areas. It seems doubtful if such readjustments, as between the continent of South America and the Caribbean islands, could be carried out without notably disturbing the relative heights of the erosion surfaces. Hence it is necessary to find a mechanism which would produce considerable eustatic lowering of the sea-level without relative vertical displacement of the land masses.

Heezen's[8] hypothesis of an expanding Earth, associated with the opening and widening of oceanic rifts, shows promise of providing such a mechanism. It is clear that, according to this hypothesis, every stage in the widening of the rift zones would add capacity to the ocean basins and thus would cause a lowering of sea-level.

A first approximation from available data indicates that a widening of the rift zones of about 150 km. would produce about 500 m. fall in sea-level. This is, of course, only a rough estimate; but it does indicate that the order of magnitude is reasonable. As Heezen points out, the Iceland graben is opening at the rate of 3·5 m. per kilometre width per thousand

years. Hence, it is not at all unreasonable to postulate widening of the oceanic rift zones by considerably more than 150 km. since middle Miocene time.

The interest in these observations is two-fold: (1) from the more general point of view, there is the further evidence of large eustatic lowering of sea-level since the middle Miocene and a possible mechanism to account for it; (2) from the regional point of view, there is the implication that the Caribbean, a tectonically active area, has suffered negligible vertical differential movements since the Miocene, and hence it would appear that any large displacements of more recent date must be confined to those in the horizontal direction.

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## CHEMISTRY

### Comparison of Helium and Argon in Ionization Detectors

R. BERRY[1] has recently directed attention to the use of helium in place of argon in a conventional argon detector. All the rare gases should behave in the same manner as argon, that is, collision of metastable rare gas atoms with molecules of other gases should deactivate the metastables with the possibility of forming ions from the colliding molecules in the appropriate conditions.

Owing to the high ionization potential of metastable helium atoms, it should be possible to arrange conditions so that a collision with one of these will ionize all other molecules except neon. As has been pointed out, however, cylinder helium contains far too many impurities for this effect to be noticed, and it is obvious that a very considerable purification process has to be set up to obtain helium sufficiently pure for the effect to be observed. This purification process is regularly done by the British Oxygen Company, the prime use for the gas so produced being in discharge tubes and the electronics industry.

It was decided, however, to see whether this helium was of sufficient purity for an argon-type detector to be useful. The results can now be compared with the information given by Berry. The helium used in this work was analysed by conventional means and the results are shown in Table 1.

Table 1. ANALYSIS OF PURE HELIUM

| | $H_2$ | $O_2$ | $CO_2 + CH_4$* | $H_2O$ |
|---|---|---|---|---|
| Concentration in v.p.m. | < 1 | < 2 | 2·3 | < 3 |

* See text.

The oxygen was determined by Hersch cell and the carbon dioxide and methane (a term used here to include all other carbonaceous material) after oxidation to carbon dioxide, by titration, the method having been checked previously against infra-red. The notable absentee in the analysis is the neon content. The helium used here was not analysed for neon. Analyses for this gas have been carried out on previous batches by mass-spectrograph, but neon was not detected. None the less, it is possible that the differences in neon content can affect the results obtained and that discrepancies between my work and that of Berry could be explained on that basis.

The apparatus used included the normal argon cell (Type *IE*.10) as manufactured by Gas Chromatography, Ltd., and the electronic equipment was one of their standard amplifiers (Type *IE*.11) modified by having an input impedance of only 71 megohms. There was no linearizing resistance in the ordinary sense, only a resistance of about 20 megohms to protect the grid of the electrometer valve.

It should be pointed out, however, that in all cases where the properties of ionization detectors are being investigated, the inclusion of both linearizing and input impedances affects the voltage across the cell once the current approaches a certain figure. As can be seen from Table 3, currents of approximately 1 gamp. are developed in the detector. This means that the resistance of the cell is about $10^9$ ohms, a figure comparable with the value[1] of the linearizing resistance used by Dr. Lovelock in his original argon detector and, so far as can be gathered, in many other versions of this instrument, and it is of such magnitude that even an input impedance of $10^8$ ohms can cause the potential across the cell to be substantially less than the apparent applied potential. However, this only applies here when the maximum current is flowing and, for the purposes of most of my experiments, the total impedance of 91 megohms can be ignored compared with the resistance of the cell.

Table 2 gives standing currents and noise-levels for both helium and argon and Table 3 gives typical results for permanent gases in helium and hydrocarbons in argon.

Table 2

| Voltage | Standing current $\times 10^{-8}$ amp. Helium | Argon | Noise $\times 10^{-10}$ amp. |
|---|---|---|---|
| 100 | 0·5 | 3·1 | — |
| 400 | 1·2 | 3·2 | — |
| 600 | 6·6 | 3·3 | ± 2·0* |
| 700 | 28 | — | — |
| 1,000 | — | 4·5 | ± 0·6† |
| 1,400 | — | 9·2 | — |

* Theoretical value ± 0·7.
† Theoretical value ± 0·5.

Table 3

| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|
| Gas | In | Max. current $\times 10^{-8}$ amp. | Dilution at max. $\times 10^{-4}$ v/v | Linear from $\times 10^{-4}$ v/v | v.p.m. current $= 10^{-6}$ amp. | | Limit of detection v.p.m. |
| $H_2$ | He | 71 | ~ 10 | * | ~ 0·05 | 1·01 | 0·4 |
| $N_2$ | He | 80 | 7·5 | * | 0·14 | 1·02 | 0·1 |
| Ar | He | > 85 | > 1·7 | ~ 1·3† | 0·24 | 1·035 | 0·1 |
| $O_2$ | He | 34 | 2·5 | 4 | 0·6 | 1·09 | 0·03 |
| $CH_4$ | He | > 85 | ⩾ 1·0 | 10 | ~ 1·2 | 1·18 | 0·01 |
| $CO_2$ | He | 80 | 1·7 | 2 | 4·1 | 1·62 | 0·005 |
| $C_4H_{10}$ | Ar | 19 | ~ 10 | 31 | 0·04 | 1·01 | 0·1 |
| $C_4H_{10}$ | Ar‡ | > 85 | > 4 | 11 | 0·065 | 1·015 | 0·06 |

Readings at 600 V.

* Non-linear positively. † Not a useful range, otherwise as $N_2$, $H_2$.
‡ at 1,000 V.

The argon results give positive non-linearity above linear point, the helium results give negative, except as stated.

In Table 3, column 4 gives the dilution of the gas at maximum current; column 5 gives the dilution of the gas when the device turns linear; column 6 gives the current at 1 v.p.m. of impurity; column 7 is the (v.p.m. current + standing current) divided by

the standing current (see Berry[1]). These results were obtained by a dilution technique.

It is immediately apparent from these results that the sensitivity and linearity of different gases varies enormously in contradiction to the implication given by Berry. On the other hand, the current at 1 v.p.m., with many of the gases tested, was much higher than the figures he quotes. It seems reasonably certain that this gas is substantially purer than the helium used by Berry. The figures in Table 2, particularly the large increase in standing current with increase in voltage, indicate that there are residual impurities in the helium, but that they can easily be accounted for by the "$CO_2$ plus $CH_4$". It is thought likely that water gives a high current in helium, and this will also undoubtedly contribute to the standing current. From the cross-section of helium, compared with that of argon, and the characteristics of the cell in argon, the standing current of pure helium at voltages less than 1,000 should be about $0{\cdot}5 \times 10^{-9}$ amp. If this is so, then the ultimate sensitivity of this device is likely to be at least ten times higher than the argon detector, owing to the much greater currents produced in helium.

The sensitivity at 700 V. is increased approximately in proportion to the increased standing current, but it is thought that the linearity is somewhat better at a higher voltage. Linearity may be improved by further purification.

The linearities given in Table 3 have been confirmed by injecting known quantities of gas directly on to a chromatograph. The peak heights and areas are in complete agreement with the results of Table 3.

As regards the quantity of gas that can be injected into the chromatograph, it is difficult to compare my results with those of Berry. He gives no indication of flow-rates, retention times, etc., but in my work, oxygen reaches the limit of its linear range with about 1 μl., while nitrogen has not reached saturation limit with 6 μl. My column was 4 ft. long, 4 mm. diameter, packed with Linde molecular sieve, and it was operated at a room temperature and a helium flow-rate of about 130 c.c./min. Oxygen took about 20 sec. to emerge and nitrogen about 90 sec.

There were one or two small pieces of rubber tubing in the apparatus used which, it was felt, might contribute to the standing current. A new apparatus is being devised in which these are eliminated and further tests are to be carried out. It is certain, however, that helium of sufficient purity to obtain the sensitivity which one would expect from this type of device can be prepared. There is no doubt that this device is an extremely sensitive one.

In conclusion, it should be pointed out that the process of purification of the helium may be followed by using a detector cell of this type. As the purity of the helium rises, so does the standing current. At this stage the injection of a quantity of permanent gases or other substances produces a drop in current (cf. Willis organic bleed). As the level of impurities falls, the current rises and eventually passes a maximum. After this point, injections of substances produce a W-shaped peak with more and more on the positive side as the purity rises further.

Finally, large positive peaks of sufficient linearity are obtained.

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It is interesting to learn that Wiseman has obtained experimental results in general confirmation of my own. The only discrepancy concerns the sensitivity ratio for the different gases. Wiseman finds this ratio to increase through the series nitrogen, argon, oxygen, methane from 1·02 to 1·18, whereas I found the same value (1·05) for all four gases. Certainly some variation would be expected, but there is insufficient basic information available to permit this to be estimated with precision. One can say, however, on the basis of the work of Jesse and Sadauskis, that carbon dioxide would not be expected to give as high a value as 1·62, which Wiseman reports.

If no other factors interfere, the value of this ratio, for a given gas, should decrease as the impurity content of the helium increases. Since my result lies between the extremes quoted by Wiseman, deductions of the relative purity of his helium and mine cannot be made in this way. Neither does the analysis of the helium by conventional means give much help; my analysis ($H_2$, $N_2$, $O_2$, Ar and $H_2O$ all $< 1$ v.p.m.) indicates that my helium carrier gas was of the same order of purity as Wiseman's. Since the methods are all at their limits of detection and, at these levels, contamination is very difficult to avoid, comparison is not really profitable.

It may be relevant that my method of determining the sensitivity ratio is to introduce sample volumes from 0·005 μl. (S.T.P.) upwards of the foreign gas into the helium immediately ahead of the column. Wiseman, since he injects quantities not less than 1 μl., must necessarily use a less-direct method of calibration, involving more lengthy extrapolation. It is encouraging that, despite these differences, our estimates of detection limits are of the same order of magnitude.

If helium requiring no further purification can be supplied at a price which is not prohibitive, the applicability of this method of detection will obviously be enhanced.

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## Determination of Uranium as Pyrophosphate

In the gravimetric determination of uranium as phosphate, the ignited precipitate is commonly considered[1] to be the pyrophosphate $(UO_2)_2P_2O_7$ (U = 66·67 per cent). In recent work in these laboratories uranium was precipitated at *p*H 5·5 from solutions containing ethylenediammetetraacetic acid, nitric acid and ammonium sulphate. The results were consistently low by 2·3 per cent relative when the precipitate was ignited to constant weight at 850° C.[2] and calculations made on the basis of the formula $(UO_2)_2P_2O_7$. As no significant quantities of uranium could be detected in the filtrates to explain the low results, the ignited precipitates were examined. They were dissolved in concentrated phosphoric acid and the solutions titrated with standard potassium dichromate solutions. From the observed titrations it was calculated that the ignited precipitates contained 33·2 ± 0·3 per cent quadrivalent uranium. For precipitates ignited at 1,000° C. the corresponding result was 33·9 ± 0·1 per cent quadrivalent uranium.

From these results it is apparent that the ignited compound cannot be represented by $(UO_2)_2P_2O_7$ and

the most probable formula is $UO.UO_2.P_2O_7$ ($U^{4+}$ 34·10 per cent; total U 68·205 per cent). Supporting evidence has been obtained by thermogravimetric analysis, but attempts to use X-ray diffraction were unsuccessful because of the non-crystalline nature of the compound.

The precipitate of uranyl ammonium phosphate is crystalline, settles readily and is easy to filter and wash.

Using the formula $UO.UO_2.P_2O_7$, quantitative recovery of uranium has been obtained from solutions of known uranium content. The results obtained on a variety of impure uranic solutions have shown good agreement with those obtained using cellulose chromatography and final weighing as $U_3O_8$.

An account of this work will be published in detail elsewhere.

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## Control of Self-heating and Gas Emission in Nitrate-containing Fertilizers

The concentration of plant food in mixed fertilizers can be increased by the replacement of ammonium sulphate, wholly or in part, by ammonium nitrate. Granular mixtures made, *inter alia*, from ammonium nitrate and superphosphate (a mixture of monocalcium phosphate and calcium sulphate) have been found to undergo spontaneous heating when stored in large heaps, rises in temperature of 20–30 deg. C. being recorded over periods of weeks.

This spontaneous heating is accompanied by the evolution of gas, and, by measuring the rate by a simple manometric technique, we have studied factors affecting the self-heating reactions. The rate of the reaction increases with the acidity and decreases with increasing moisture content of the fertilizer. A decrease of the acidity of the mixture, sufficient to prevent self-heating, leads to a large and undesirable loss in the water-solubility of the phosphate component owing to the formation of dicalcium phosphate. An increase in the moisture content of the fertilizer is not practicable, as it increases the tendency of the mixture to cake.

Phosphate rocks contain small amounts of organic matter of unknown composition[1], and we have confirmed that this material is not destroyed during the manufacture of superphosphate. Typical amounts of organic matter in some superphosphates used in the production of fertilizers in the U.K. are shown in Table 1.

Table 1. Organic Matter in Superphosphates

| Source of rock for superphosphate | Organic matter content (per cent carbon) |
|---|---|
| Morocco | 0·10 |
| Nauru | 0·40 |
| Florida | 0·16 |
| Gafsa | 0·50 |

In a mixed fertilizer made, *inter alia*, from ammonium nitrate and one of these superphosphates, it might be expected that the organic matter would be oxidized by the nitrate under acidic conditions. We have shown that the gas evolved from the fertilizer consists mainly of carbon dioxide and nitrogen (ratio approx. 1 : 5), together with small amounts of nitrogen dioxide. Acidified mixtures of some organic materials and ammonium nitrate also liberate these gases. Powdered coal reacts similarly when incorporated into a nitrate-containing fertilizer. The amount of carbon dioxide evolved from the fertilizers shows that oxidation of the organic material is far from complete, and thermo-chemical calculations on model organic systems (for example, polynuclear hydrocarbons) show that partial oxidation, to products such as phthalic acid, would liberate sufficient heat to explain the observed rises in temperature.

The self-heating of nitrate-containing mixed fertilizers may be reduced by removing, or modifying, the organic material. We have achieved this by calcining the initial rock at temperatures of 800–1,000° C. and by other means involving oxidation of the organic matter before the superphosphate is mixed with the other components[2]. Of these methods, calcination is undesirable, as it decreases the reactivity of the rock towards sulphuric acid in superphosphate manufacture.

The auto-oxidation of some organic nitro-compounds can be prevented by the addition of substituted ureas or secondary amines[2], and we have found that addition of small amounts of urea, 0·25–0·75 per cent by weight, to mixed fertilizers effectively reduces the oxidation of the organic matter and hence the self-heating of the fertilizers[3]. The effect of urea on the reactivity of laboratory-prepared samples of a mixed fertilizer (N, 10 per cent : $P_2O_5$, 10 per cent : $K_2O$, 18 per cent) containing 20 per cent ammonium nitrate is shown in Table 2. Each fertilizer contains 0·25 per cent urea, and the activity of the material is assessed in terms of the gas pressure developed in 48 hr. at 50° C.

Table 2. Effect of Urea on the Reactivity of a Mixed Fertilizer

| Source of phosphate rock | Percentage reduction in reactivity |
|---|---|
| Morocco | 70·5 |
| Florida | 88·5 |
| Nauru | 92·0 |

Incorporation of urea into these fertilizers also has a marked effect on the release of nitrogen dioxide. Table 3 shows results obtained with a mixed fertilizer (N, 10 per cent : $P_2O_5$, 10 per cent : $K_2O$, 18 per cent), the nitrogen dioxide being evolved into a stream of air drawn through the fertilizer.

Table 3. Effect of Urea on the Evolution of Nitrogen Dioxide

| Source of rock for superphosphate | Urea content (per cent) | $NO_2$ evolved (ml./kgm. fertilizer) in 14 days |
|---|---|---|
| Nauru | 0·0 | 120·7 |
| Nauru | 0·10 | 28·7 |
| Nauru | 0·50 | 19·7 |
| Morocco | 0·0 | 49·3 |
| Morocco | 0·25 | 9·3 |
| Morocco | 0·50 | 4·0 |

The oxidizing action of nitric acid involves the presence of trace amounts of nitrous acid, probably in the form of the nitrosonium ion[4]. It seems likely that, in the oxidation process we have studied, nitrous acid is formed autocatalytically, so that it should be possible to suppress the oxidation by removing the nitrous acid with, for example, urea. A small quantity of urea should be adequate to prevent the oxidation, and, in fact, we have observed

no appreciable loss during long-term storage of fertilizers. The rate of the urea/nitrous acid reaction is undoubtedly fast enough to explain this inhibition effect[5]. It is well known that the oxidation of organic compounds during nitration can be prevented by the addition of small amounts of urea[6].

So far, approximately 1·25 million tons of mixed fertilizers containing urea as an inhibitor have been produced and have shown satisfactory storage properties, both in large heaps and in paper sacks. At the elevated temperatures attained in the absence of urea the caking tendency is increased, causing subsequent difficulty in reclaiming from the heap. Storage of the untreated fertilizer in paper sacks causes severe chemical attack on the paper (due to nitrogen dioxide) with subsequent breaking of the sacks when moved.

In conclusion, it may be noted that self-heating of fertilizer storage heaps can also occur if inter-ionic reactions (for example, between ammonium nitrate and potassium chloride) take place. Results of investigations into this problem, and a more detailed account of the urea inhibition work, will be published elsewhere.

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## Solid Solutions in the System Ammonium Nitrate–Potassium Nitrate

By phase work on the system ammonium nitrate–potassium nitrate–water, Janecke[1,2] showed that below 23° C. two types of solid solution can exist: potassium nitrate dissolved in ammonium nitrate (form III) and ammonium nitrate in potassium nitrate (form II). At higher temperatures there is an increasing amount of another phase which is of a different crystalline form from any of the normal modifications of the two salts. Janecke suggests that this phase is a solid solution of ammonium nitrate in a metastable form of potassium nitrate, which is only formed on cooling, in the temperature-range 128°–115° C.

By using X-ray diffraction measurements, Janecke's suggestion has been confirmed. Further, the limits of the composition of the solid solution have been determined and also its heat of formation from the individual salts.

Aqueous solutions of ammonium and potassium nitrates were evaporated to dryness at various temperatures between 25° and 120° C. After cooling, diffraction patterns were obtained using a Geiger diffractometer, radius 24 cm.; the radiation was copper $K\alpha$, the $K\beta$ component being removed by a nickel filter. From the diffraction patterns, the relative abundance of each phase was determined.

Samples produced at temperatures of 100° C. and above, from equimolar mixtures of the two salts, consisted almost entirely of a phase having a diffraction pattern similar to that found by Kracek *et al.*[3] and by Barth[4] for the metastable form of potassium nitrate. Hereafter, this phase will be referred to as ($x$KNO$_3$.NH$_4$NO$_3$). If more ammonium nitrate is added to an equimolar mixture, it does not dissolve in this phase, and increasing amounts of ammonium nitrate (form III) containing dissolved potassium nitrate are found. Thus, in ($x$KNO$_3$.NH$_4$NO$_3$) the value of $x$ cannot decrease below approximately 1. When the molar ratio of potassium nitrate to ammonium nitrate is greater than one, the mixture still consists essentially of a single phase having a very similar diffraction pattern. In the phase ($x$KNO$_3$.NH$_4$NO$_3$), $x$ can rise to a maximum of approximately 3, this change being accompanied by a slight shift in the diffraction pattern. In Table 1 the unit cell dimensions found for solid solutions of composition (3KNO$_3$.NH$_4$NO$_3$) and (KNO$_3$.NH$_4$NO$_3$) are compared with those of the high temperature and metastable forms of potassium nitrate; Table 2 shows the corresponding diffraction patterns. All lines are listed up to a maximum Bragg-angle of 35°, the values of '$d$' being accurate to 0·01 Å.

Table 1. Unit Cell Dimensions of the High-Temperature Forms of Potassium Nitrate, and Related Solid Solutions

| Material | Space group | Cell size: Hexagonal axes (3 moles/cell) | Cell size: Rhombohedral axes (1 mole/cell) |
|---|---|---|---|
| KNO$_3$ (form I) at 130° C. | $D^{\ }_{3d}$ — $R\bar{3}m$ | $a$ = 5·44 Å.<br>$c$ = 9·76 Å. | $a$ = 4·54 Å.<br>$\alpha$ = 73° 24′ |
| KNO$_3$ (metastable) at 120° C. | $C^{\ }_{3v}$ — $R3m$ | $a$ = 5·48 Å.<br>$c$ = 9·27 Å. | $a$ = 4·42 Å.<br>$\alpha$ = 76° 42′ |
| NH$_4$NO$_3$.3KNO$_3$ at 20° C. | $C^{\ }_{3v}$ — $R3m$ | $a$ = 5·52 Å.<br>$c$ = 9·09 Å. | $a$ = 4·38 Å.<br>$\alpha$ = 77° 42′ |
| NH$_4$NO$_3$.KNO$_3$ at 20° C. | $C^{\ }_{3v}$ — $R3m$ | $a$ = 5·56 Å.<br>$c$ = 9·12 Å. | $a$ = 4·42 Å.<br>$\alpha$ = 77° 54′ |

The chief difference between the patterns of potassium nitrate (form I) and potassium nitrate (metastable) is the absence of the (0003) reflexion in that of the former. The presence of this reflexion in all patterns from the phase ($x$KNO$_3$.NH$_4$NO$_3$) indicates that its structure is derived from that of the metastable form. When solutions of composition (KNO$_3$.NH$_4$NO$_3$) and (3KNO$_3$.NH$_4$NO$_3$) are heated to 130° C., the diffraction patterns show that there is an abrupt expansion of the lattice, and a total disappearance of the (0003) line, that is, the transition to potassium nitrate (form I), occurs.

When ammonium and potassium nitrates react at temperatures below 100° C. the extent of conversion to the phase ($x$KNO$_3$.NH$_4$NO$_3$) is considerably less, and increasing amounts of ammonium nitrate (form III), containing dissolved potassium nitrate, are found. There is also a tendency for $x$ to have a value less than the maximum possible.

The X-ray measurements show that the solution of ammonium nitrate in the metastable form of potassium nitrate causes the lattice to expand. This is to be expected, since the ammonium ion (radius 1·42 Å.) is slightly larger than the potassium ion (radius 1·33 Å.). On cooling metastable potassium nitrate the lattice contracts until, at approximately 115° C., it collapses into a more compact form. This change is delayed by the replacement of potassium by larger ions, and in the case of ammonium ions the change does not occur on cooling to room temperature. The stability of the solid solution increases

Table 2. INDICES

| Hexagonal axes | Rhombohedral axes | $KNO_3$ (form I) at 130° C. | | $KNO_3$ (metastable) at 120° C. | | $NH_4NO_3.3KNO_3$ at 20° C. | | $NH_4NO_3KNO_3$ at 20° C. | |
|---|---|---|---|---|---|---|---|---|---|
| | | $d$.Å. | $I$rel. | $d$.Å. | $I$rel. | $d$.Å. | $I$rel. | $d$.Å. | $I$rel. |
| 10$\bar{1}$1 | 010 | — | — | 4·22 | 1 | 4·22 | 1 | 4·26 | 3 |
| 01$\bar{1}$2 | 110 | 3·38 | 100 | 3·32 | 100 | 3·30 | 100 | 3·31 | 100 |
| 0003 | 111 | absent | absent | 3·09 | 80 | 3·03 | 51 | 3·04 | 59 |
| 11$\bar{2}$0 | 01$\bar{1}$ | 2·72 | 22 | 2·74 | 27 | 2·77 | 28 | 2·78 | 35 |
| 02$\bar{2}$1 | 11$\bar{1}$ | 2·29 | 15 | 2·30 | 12 | 2·32 | 35 | 2·33 | 47 |
| 20$\bar{2}$2 | 020 | 2·12 | 13 | 2·11 | 13 | 2·11 | 21 | 2·13 | 33 |
| 10$\bar{1}$4 | 121 | 2·17 | 33 | 2·08 | 35 | 2·05 | 31 | 2·06 | 29 |
| 11$\bar{2}$3 | 120 | 2·08 | 17 | 2·05 | 18 | 2·05 | | 2·05 | 33 |
| 21$\bar{3}$1 | 021 | 1·75 | 4 | 1·76 | 1 | 1·77 | 5 | 1·78 | 9 |
| 01$\bar{1}$5 | 221 | 1·80 | 2 | 1·72 | 3 | 1·69 | 8 | 1·70 | 9 |
| 12$\bar{3}$2 | 121 | 1·67 | 3 | — | — | 1·69 | | 1·70 | |
| 30$\bar{3}$0 | 11$\bar{2}$ | 1·61 | 2 | 1·58 | 0·5 | 1·59 | 1 | 1·60 | 1 |
| 21$\bar{3}$4 | 130 | 1·44 | 3 | 1·42 | 0·5 | 1·41 | 6 | 1·42 | 11 |
| 30$\bar{3}$3 | 030 | 1·41 | 1 | 1·41 | 0·5 | 1·41 | | 1·42 | |
| 22$\bar{4}$0 | 022 | 1·36 | 1 | 1·37 | 0·5 | 1·38 | 1 | 1·39 | 1 |
| 1126 | 231 | 1·40 | 2 | — | — | — | — | — | — |

as more ammonium ions are added, and it is for this reason that there is a tendency for potassium nitrate to crystallize out from the phase ($3KNO_3.NH_4NO_3$), thereby increasing its content of ammonium ions. In the presence of traces of water, the phase ($xKNO_3.NH_4NO_3$) is unstable at room temperature and changes into solid solutions of potassium nitrate in ammonium nitrate (form III) and ammonium nitrate in potassium nitrate (form II).

The heats of solution in water of the phases ($KNO_3.NH_4NO_3$) and ($3KNO_3.NH_4NO_3$) were found to be − 13·4 and − 28·5 k.cal./mole respectively. In each case the material contained approximately 95 per cent of the phase ($xKNO_3.NH_4NO_3$). Using existing values for the heats of solution of potassium and ammonium nitrates, the heats of formation of the two solid solutions from the individual salts were calculated to be − 1·4 and − 3·2 k.cal./mole respectively. These values are accurate to within ± 10 per cent, and are comparable with that for the transition from the high- to the low-temperature form of potassium nitrate, + 1·19 k.cal./mole.

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## Banded Spherulites of Hippuric Acid

IT has long been known that under certain conditions many substances crystallize in the form of spherulites showing concentric extinction bands between crossed polars. The explanation of this effect, originally put forward by Michel-Levy and Munier Chalmas[1] for chalcedony, and later confirmed by other workers[2–5] for a number of substances of low molecular weight, was that the structure of the spherulite has a twist around any given radius, and that the bands correspond to those orientations in which an optic axis is parallel to the light beam. Thus, Gaubert[5] obtained spherulites of hippuric acid in which the radial twist was around the β-axis of the indicatrix, a fact which he established conoscopically, that is, by a study of the interference figures along the radii. More recently there has been a revival of interest in banded spherulites, since they are formed by many polymers (for example, polythene and terylene). These cases have been the subject of much investigation by, among others, Keller[6], and Point[7], who have shown convincingly, from the optical effects of tilting the preparations with respect to the direction of the light, that the spherulites have a radially twisted structure as for the low molecular weight substances referred to above.

In the course of a student's exercise in this Department on the crystal optics of hippuric acid we recently obtained (i) a spherulite, part of which showed a well-defined radial twist around the β-axis as observed by Gaubert (Fig. 1), and also (ii), on another preparation, a number of complete spherulites showing a radial twist around the α-axis (Fig. 2), in both cases as a result of allowing a melted film between a slide and cover slip to crystallize spontaneously on a slowly cooling metal plate. The existence of both kinds of twists, and also their sense, have been established directly from the interference figures shown by the spherulites at successive points along their radii. The figures were particularly clear in (i), in which the pitch of the twist was large (about 1 mm.). Different stages in the twist (right-handed in this case) along one radius are pointed out in Fig. 1; thus, starting with the central emergence of an optic axis $A_1$ (extinction band in parallel light), we pass in succession to an acute bisectrix view ($Bx_a$), the central emergence of the other optic axis $A_2$ (extinction band again), an obtuse bisectrix view ($Bx_o$), and, completing a rotation of 180°, axis $A_1$ again, and so on. (In Fig. 1 as reproduced the extinction bands are not appreciably darker than the bands marking the 'sensitive violet' tint between first order red and second order blue.) In confirmation of the evidence afforded by the interference figures, two determinations of the ratio of the path differences for adjacent $Bx_o$ and $Bx_a$ regions by means of a graduated quartz wedge gave values of 3·0, 3·1, while that calculated from the published refractive indices[8,9] is 2·9. Furthermore, rough measurements of the ratio of adjacent wide and narrow spacings of the extinction bands on Fig. 1 give an average value of 1·7, which agrees with that given by the published figure, 66°, for 2 V.[8,9].

In case (ii) (Fig. 2) there are no extinction bands, because the twist results in an alternation of the $Bx_a$ (with β now normal to the twist axis) and optic normal views, and at no point does an optic axis

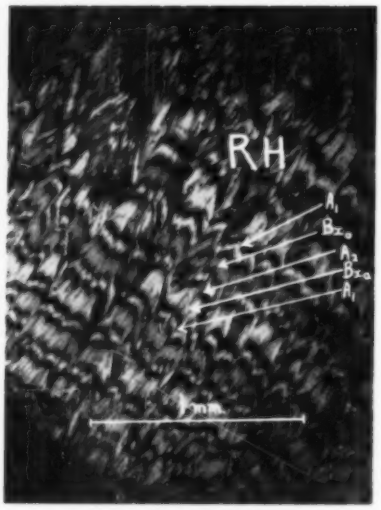


Fig. 1. Portion of spherulite showing radial twist about *z*-axis. Sense of twist right-handed (*RH*)

become vertical. Both right-handed and left-handed twists were found as indicated on the figure. The nature of the twist was confirmed by determinations of the path differences of adjacent optic normal and $Bx_a$ regions, by direct identification of the polarization colours for the thicker spherulites, and by means of the graduated quartz wedge for thinner sections. Values of the ratio of these path-differences obtained were: 4·0, 3·9, 4·0; that calculated from the refractive indices is 3·9. The pitch was smaller than in (i) (for example, about 0·2 mm. for the middle region of the large central spherulite in Fig. 2) and it decreased as the borders of the spherulites were approached, that is, in the direction of falling temperature of growth. In some cases the prominent bands ceased altogether at the borders of the spherulite, and gave place to a more or less uniform structure

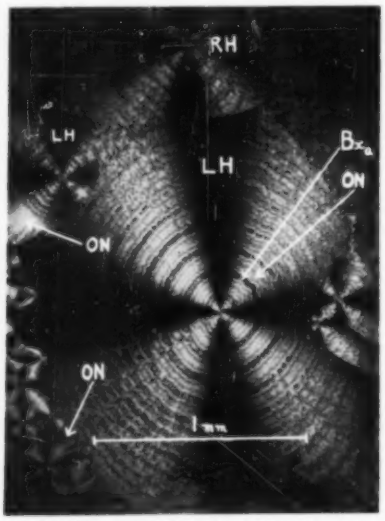


Fig. 2. Spherulites showing radial twist around *a*-axis. Both right-handed (*RH*) and left-handed (*LH*) spherulites present

which showed an optic normal interference figure. Examples are the two areas marked *ON* (optic normal) on the left of Fig. 2. These may have been regions in which the twisting process had ceased, or, more probably in view of the decreasing pitch in the regions which immediately preceded them, in which the pitch had become smaller than the limit of resolution of the microscope, so that the refractive index for light vibrating normally to the radii of the spherulites was an averaged value between $\beta$ and $\gamma$. Whatever the explanation, it is probable that it applies also to the small unbanded spherulites seen along the left-hand margin of Fig. 2.

The spherulites of both types (i) and (ii) had a markedly fibrous structure radially, as is commonly observed in spherulites, and it is of course possible that in these structures we are dealing with twisted linear aggregates of very narrow acicular crystals, which, individually, have little or no twist.

It is of interest that for both types the optical evidence suggests that it is the long axis of the molecule (presumably parallel, or nearly so, to the *c* direction) which is oriented tangentially, as is the case in polymer spherulites.

Finally, it may be noted that hippuric acid belongs to class 222, one of the enantiomorphous symmetry classes[8]. Gaubert[5] was of the opinion that membership of such a class was conducive to the formation of twisted structures. It is tempting to go further, and suggest that the right- and left-handed spherulites are based respectively on the two enantiomorphous forms of the crystal.

I thank Dr. Keller for directing my attention to Gaubert's earlier work on hippuric acid.

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## BIOCHEMISTRY

### Nucleotides and Other Phosphorus Compounds of Cockroach Nerve

A NUMBER of phosphorus compounds, some of which have a vital role in vertebrate nerve function, have been demonstrated in the abdominal part of the ventral nerve cord of adult male *Periplaneta americana*. An estimate of their relative tissue concentrations has been made by the labelled pool technique[1]. Groups of about ten cockroaches were injected with 400 $\mu$c. of carrier-free phosphorus-32 orthophosphate per individual. They were held for seven days on normal diet to permit equilibration between injected phosphorus-32 and phosphorylated metabolites. Part of the nerve cord of each animal was exposed *in situ* by removing a strip of abdominal wall, separated from the animal by a piece of black paper and dissected free from other tissues, haemolymph being washed off with Ringer solution. The cord was monitored using a cathode ray oscilloscope

to ensure that it was capable of conducting impulses. Each electrically normal cord was raised up on two hooks 8 mm. apart, and the preparation flooded with liquid nitrogen. The frozen cord sample was transferred quickly to a homogenizer tube itself immersed in liquid nitrogen. After breaking up the tissue in 50 per cent ethanol made 1 *N* with respect to formic acid, the homogenizer was kept at −30° C. for 15 min. to allow thorough penetration of the medium. The tissue was warmed to 5° C., thrice extracted with 0·2 ml. extraction medium, and the extract separated by paper and elution[2] chromatography into a number of fractions. By automatic scanning of paper chromatograms[1] and Geiger counting of column effluents in solution, the size of each fraction was estimated, the results being expressed as percentages of the extracted phosphorus-32. The principal constituents of the extract were identified by co-chromatography with known substances. Where a fraction was shown to contain substantial impurity, the fact is indicated in Table 1 by a question mark and a 'less than' sign, though there may be small amounts of unidentified material in any fraction. About 60 per cent of the total phosphorus-32 of the nerve is extracted by the above procedure. The total phosphorus of cockroach abdominal nerve cord was found to be 1·41 mgm./gm. wet weight using the method of Bartlett[3]. In calculating approximate tissue concentrations of substances from these data, it has been assumed that the quantities of phosphorus-32 assayed reflect the amounts of phosphorus-31 present, both in the extract and in the insoluble residue. This assumption is not strictly valid, so the figures quoted (Table 1) are an indication of the order of magnitude of concentration of the metabolites listed.

Using an independent technique based on perchloric acid extraction and firefly luciferin assay the level of adenosine triphosphate in cockroach nerve was found to be 1,350 µgm./gm. wet weight.

In some experiments an unlabelled extract was prepared from lobster, *Homarus vulgaris*, ventral nerve cord and added to the labelled cockroach extract to reduce adsorption losses during column chromatography. This precaution proved to be unnecessary, but six compounds, coenzyme 1, cytidine monophosphate, adenosine mono-, di- and tri-phosphates, and uridine diphosphate, were tentatively identified by co-chromatography in the lobster nerve extracts.

Table 1

| | Percentage of extracted phosphorus-32 (No. of observations) | Approximate tissue concentration (µgm. gm. wet weight) |
|---|---|---|
| Adenosine-5-phosphate | 0·3 (3) | 30 |
| Adenosine-5-diphosphate | 3·0 (7) | 180 |
| Adenosine-5-triphosphate | 18·5 (6) | 850 |
| Cytidine-5-phosphate | 0·2 (3) | 20 |
| Cytidine-5-diphosphate + ? | 2·2 (6) | < 120 |
| Cytidine-5-triphosphate | 2·4 (6) | 100 |
| Guanosine-5-diphosphate | 1·1 (4) | 70 |
| Guanosine-5-triphosphate | 1·8 (3) | 90 |
| Uridine-5-diphosphate | 1·5 (6) | 80 |
| Uridine-diphospho-glucose | 1·2 (6) | 90 |
| Uridine-5-triphosphate | 3·4 (3) | 150 |
| Co-enzyme 1 | 2·3 (7) | 210 |
| Co-enzyme 2 + ? | 0·5 (6) | < 30 |
| Orthophosphate | 25·4 (6) | 660 |
| Glucose-6-phosphate | 1·1 (3) | 80 |
| Arginine phosphate | 7·8 (2) | 540 |
| α-Glycerophosphate + ? | 3·7 (6) | < 170 |
| Unidentified fractions | 33·6 | |
| | 100·0 | |

Ethanolamine phosphate, riboflavin phosphate, guanosine monophosphate, uridine monophosphate and inosine monophosphate were not detected

A full account of this and related work will be published elsewhere. We are indebted to Dr. P. C. Caldwell for a gift of arginine phosphate and to Dr. N. Frontali for help in two experiments.

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## Incorporation of Amino-Acids into Protein and Ribonucleic Acid of the Lens of the Rat; Effect of Heavy Metals

The distribution of nucleic acids and proteins within the cell varies from organ to organ. Tissues rich in ribonucleic acid (RNA) are particularly active in protein synthesis, thus indicating a close association between protein synthesis and RNA concentration[1–3]. Work from several laboratories now clearly shows that RNA is one of the essential components for protein synthesis[2–4]. Because of the relatively high concentration of RNA[5–7] and protein[8], and the absence of enzyme systems to hydrolyse adenosine triphosphate (ATP) and guanosine triphosphate (GTP) in the ocular lens[9,10], this organ may offer certain advantages for the investigation of protein biosynthesis as compared with a more complex organ such as the liver.

In order to investigate the incorporation of amino-acids labelled with carbon-14 into lens protein and RNA, lenses derived from Holtzman strain white male rats (6 weeks of age and weighing approximately 80 gm. each) were used. For the *in vitro* experiments these lenses were removed immediately after the animals were killed, weighed, and homogenized in Dounce microhomogenizers[11] at 0° C. in a medium consisting of 7 parts 0·03 *M* sucrose, 1 part 0·025 *M* potassium chloride and 1 part 0·03 *M* potassium bicarbonate. The capacity of such a system to catalyse the incorporation of $^{14}$C-leucine, valine or histidine into lens RNA and proteins, and the experimental conditions, are summarized in Table 1.

Although the incorporation of amino-acids can occur over a broad *p*H range, from *p*H 6·0 to 10·0, all the foregoing experiments involving $^{14}$C-leucine and valine were carried out at *p*H 8·5 in 0·1 *M tris* buffer since this was the *p*H optimum for the incorporation of these two amino-acids. The corresponding optimum *p*H for histidine was 9·0 and the experiments involving this amino-acid were all performed at this *p*H.

Incorporation of $^{14}$C-leucine, valine or histidine into lens proteins and RNA could also be demonstrated by the injection of these amino-acids intraperitoneally into rats. The resulting *in vivo* incorporation was comparatively less than the results obtained with the *in vitro* studies, reaching a maximum 3 hr. after injection.

The results of the *in vitro* experiments carried out in the presence of cobaltous chloride are shown in Table 1. Without the addition of this metal the incorporation of carbon-14-labelled leucine, valine, or

Table 1. Incorporation of $^{14}$C-Amino-Acids into Lens RNA–Protein Complex*

(c.p.m. per mgm. of RNA–protein complex)

| | $^{14}$C-leucine range | $^{14}$C-valine range | $^{14}$C-histidine range |
|---|---|---|---|
| (*A*) | | | |
| Lens homogenate | 3 (0–3) | — | — |
| " + $Mg^{++}$ | 16 (12–19) | 9 (7–14) | 37 (33–46) |
| " + $Mg^{++}$ + ATP | 12 (19–31) | 20 (12–22) | 58 (50–62) |
| " + $Mg^{++}$ + ATP + GTP | 51 (44–57) | 50 (38–49) | 93 (90–95) |
| " + ATP + GTP | 16 (14–17) | 16 (15–17) | 21 (20–22) |
| (*B*) | | | |
| Lens homogenate + $Co^{++}$ | 540 (433–582) | 432 (410–462) | 1,252 (1,150–1,482) |
| " + Co + ATP | 730 (652–820) | 670 (630–690) | 2,058 (2,000–2,158) |
| " + Co + ATP + GTP | 575 (506–600) | 462 (442–485) | 1,320 (1,120–1,490) |

* ml. of the reaction mixture contained 0·5 ml. lens homogenate (50 mgm./ml.), 20 μmoles *tris* buffer *p*H 8·5 (for leucine and valine) or *p*H 9·0 (for histidine), 5 μmoles $Co^{++}$ (or 10 μmoles $Mg^{++}$), 10 μmoles ATP and 10 μmoles GTP (in the reactions indicated above), 0·56 μmole $^{14}$C-valine ($8{\cdot}56 \times 10^6$ c.p.m.), 0·65 μmole $^{14}$C-leucine ($1{\cdot}04 \times 10^6$ c.p.m.) or 1·30 μmoles $^{14}$C-histidine ($9{\cdot}52 \times 10^5$ c.p.m.). The reaction mixtures were incubated at 37° C. for 1 hr. and the reaction was terminated by adding 5 per cent TCA. The precipitate was washed four times with 5 per cent TCA, once with hot alcohol (50° C. for 10 min.), once with alcohol, twice with ether, and then plated and counted in a gas flow counter (Nuclear Chicago) as infinitely thick layers with a counting error of 6–8 per cent. Each result shown above represents the average value for 6–8 experiments.

histidine was low. $Mg^{++}$ can to some extent replace $Co^{++}$ but was much less effective; even by increasing its concentration ten-fold over the concentration of $Co^{++}$ it was not possible to achieve an appreciable incorporation. $Zn^{++}$, $Mn^{++}$, and $Ca^{++}$ did not have the stimulating effect of $Co^{++}$ or the inhibitory effect of $Ni^{++}$ on the incorporating system. Addition of 10 μmoles of $Ca^{++}$ in the presence of 1 μmole of $Co^{++}$ blocked 95 per cent of the incorporation of $^{14}$C-leucine into lens proteins, and even in the presence of 5 μmoles of $Co^{++}$ 90 per cent inhibition was still noted (Fig. 1).

The incorporation of labelled leucine, valine, or histidine into lens proteins and RNA was to a certain degree dependent on the addition of ATP. Furthermore, the addition of 10 μmoles of GTP instead of being stimulating actually inhibited the incorporation by 25–30 per cent. On the other hand, in experiments where $Mg^{++}$ instead of $Co^{++}$ was used, addition of ATP and GTP showed a stimulating effect. Activation of an amino-acid by *p*H 5·2 enzyme requires ATP[12] and for the transfer of the activated amino-acid from an AA-SRNA complex to ribonucleoprotein particles, both ATP and GTP are required[13]. The inhibitory action of GTP is not understood at the present time.

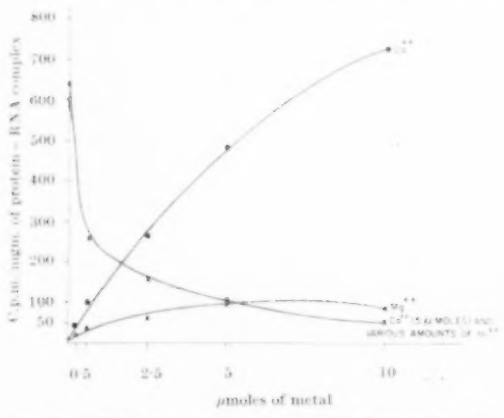


Fig. 1. Effect of $Mg^{++}$ and $Co^{++}$ with and without $Ni^{++}$ on the incorporation of $^{14}$C-leucine into lens protein and RNA. The assay method was the same as described above, except that varying amounts of $Mg^{++}$ or $Co^{++}$ were used; where the inhibitory effects of $Ni^{++}$ were studied the latter's concentration varied as shown above. The concentration of $Co^{++}$ was kept constant (5 μmoles). Every point represents an average of three separate experiments

In order to determine whether the effect of $Co^{++}$ on the amino-acid incorporating systems previously described was an artefactual one (that is, due to some form of metal substrate complexing) the following experiments were performed.

(1) Two experiments were performed in which 5 per cent trichloracetic acid was added to the incubation media prior to the addition of the labelled amino-acid. After 1 hr. incubation the recovered activity was 4·6 and 6·6 c.p.m. per mgm. protein in contrast to the 540 and 432 c.p.m. obtained in the experimental reaction (cf. Table 1).

(2) There was no incorporation of these amino-acids when the incubations were performed at 0° C.

(3) Changes in the concentration of the enzyme (lens homogenate) resulted in a linear increase in the recovery of labelled amino-acids.

(4) Two experiments were performed in which the procedure was the same as originally described, but two final washings with ethyl mercaptan were added. There was no change in the recovery of $^{14}$C-leucine following this procedure as compared with the values obtained when the ethyl mercaptan washings were omitted.

(5) In two experiments protamine sulphate was used instead of lens homogenate in the reaction mixture. No activity was recovered following the usual 1 hr. incubation.

(6) When $Co^{++}$ activation was studied in rat liver microsomes and supernatant, in the presence of ATP and GTP, the count obtained was 6–8 c.p.m. and 75–80 c.p.m., respectively.

(7) The enzymic nature of the incorporating system was further indicated by the failure of this system to catalyse the incorporation of aliphatic amines such as cadaverine, putrescene and histamine labelled with carbon-14 into lens proteins. The conditions of these experiments were similar to those described by Sarkar *et al.*[14].

The results of these foregoing experiments indicate that the effects observed with $Co^{++}$ were not artefactual. There is apparently a definitive increase in the uptake of amino-acids by lens protein and RNA which can be ascribed to $Co^{++}$.

The rat lens incorporating system is thus different from the rat liver incorporating system described by Zamecnik *et al.*[13]. The former does not require additional amounts of GTP, and unlike the latter requires $Co^{++}$ instead of $Mg^{++}$ for maximum activity. Furthermore, only 50–60 per cent of the capacity of lens protein–RNA system to incorporate amino-acids into lens proteins could be abolished by treatment with RNase prior to the addition of amino-acids. Another important property of the rat lens incorporating system is the remarkable ability of its RNA to bind amino-acids. About 80 per cent of the total amino-acid incorporated into material precipitable by trichloracetic acid is retained even after a 2 hr. incubation of the amino-acid with the rat-lens homogenate; in contrast, in the rat liver incorporating system a relatively high percentage of total amino-acid, found in TCA-precipitable material, is characteristically found in the protein fraction. Experiments are now in progress to determine whether the effect of $Co^{++}$ can be obtained in a

system in which a full complement of amino-acids are used in addition to the specific labelled ones.

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## Degradation of Deoxyribonucleic Acid in *Escherichia coli* Cells treated with Mitomycin C

IT has been shown[1,2] that treatment of growing cells of *E. coli B* (strain 9637 from A.T.C.C.) with mitomycin *C* (MC) results in inhibition of deoxyribonucleic acid (DNA) formation. The synthesis of ribonucleic acid (RNA) and protein was unaffected at low levels of MC. The addition of MC in higher concentrations also blocks the synthesis of RNA and protein.

In our work on the mode of action of antibiotics upon microbiological systems[3–5]—especially on nucleic acids—we have investigated the influence of MC on DNA, RNA and protein present in cells of *E. coli B* at the end of the logarithmic phase of growth. The strain of *E. coli B* was sensitive to MC (Fig. 1). Cells grown in a salt-glucose synthetic medium for 12 hr. at 37° C. and at *p*H 7·0 with aeration were then treated with increasing amounts of MC. Turbidity, protein, DNA and RNA were estimated in aliquots of bacterial suspensions immediately after the addition of MC and after 4 hr. and 8 hr. of incubation at 37° C. The *p*H was controlled and was found to be constant during the experiment.

Turbidity was measured photometrically at 578 mμ. Ribonucleic acid and deoxyribonucleic acid were determined after extraction (15 min. at 90° C. with 0·5 *N* perchloric acid) from acid-insoluble precipitates of bacteria with orcinol and diphenylamine respectively. The residue remaining after extraction of DNA and RNA was analysed for protein with the biuret method. The analytical values obtained in the untreated controls at the end of the experiment (8 hr.) were set at 100 and all other values were relative to them.

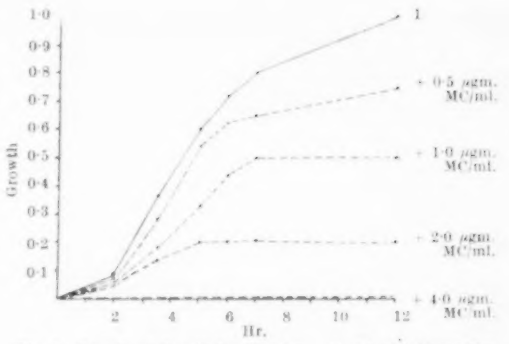


Fig. 1. Growth of *E. coli B* without (——) and with increasing amounts of mitomycin *C* added to the incubation medium (– – –). Turbidity measured at 578 mμ

After the logarithmic phase there is only a slight incline in growth of the untreated control during time of incubation (Table 1). Mitomycin added to the incubation medium at the end of the logarithmic phase of growth caused a marked drop in DNA content. After 4 hr. incubation with 2·5 μgm. MC/ml. the DNA content was reduced to 60 per cent and after 8 hr. to 37 per cent.

During this time turbidity and protein content remain constant, whereas the RNA content shows only a slight decline. Furthermore, no lysis of the cells could be observed as indicated by cell count. The bacterial suspension contained $1 \times 10^9$ cells/ml., corresponding to an optical density of 1·00 at 578 mμ. The possibility that degradation of DNA was caused by induction of phage during incubation with MC—as is the case with the lysogenic *E. coli* strain $K_{12}$ (ref. 6)—was excluded by electronmicroscopical and microbiological methods.

The remaining supernatants, after precipitationand centrifugation of DNA, RNA and protein, were checked for ultra-violet absorbancy. Aliquots taken just after the addition of MC were used for reference and the corresponding aliquots taken after 4- and 8-hr. incubation were compared with them. During incubation with MC, substances with an absorption maximum at 260 mμ appear and the $\Delta E$ values increase with increasing amounts of MC. This effect

Table 1. EFFECT OF MITOMYCIN *C* ON *E. coli B*. MITOMYCIN *C* WAS ADDED AT THE END OF LOGARITHMIC PHASE OF GROWTH (12 HR.)

| Time | μgm. MC/ml. | Turbidity (per cent) | Protein (per cent) | DNA (per cent) | RNA (per cent) | $\Delta E_{260}$ mμ |
|---|---|---|---|---|---|---|
| After 12 hr. of growth | 0 | 86 | 90 | 82 | 80 | — |
| | 0·1 | 89 | 91 | 85 | 86 | — |
| | 0·25 | 87 | 84 | 85 | 83 | — |
| | 0·50 | 89 | 82 | 84 | 89 | — |
| | 1·00 | 87 | 90 | 85 | 91 | — |
| | 2·50 | 89 | 90 | 84 | 87 | — |
| 4 hr. after addition of mitomycin *C* | 0 | 93 | 100 | 98 | 100 | — |
| | 0·1 | 96 | 100 | 97 | 95 | 0·210 |
| | 0·25 | 92 | 98 | 89 | 95 | 0·230 |
| | 0·50 | 94 | 96 | 84 | 89 | 0·380 |
| | 1·00 | 90 | 98 | 79 | 91 | 0·450 |
| | 2·50 | 88 | 88 | 60 | 80 | 0·660 |
| 8 hr. after addition of mitomycin *C* | 0 | 100 | 100 | 100 | 100 | 0·010 |
| | 0·1 | 99 | 100 | 100 | 95 | 0·440 |
| | 0·25 | 93 | 106 | 100 | 90 | 0·650 |
| | 0·50 | 90 | 98 | 72 | 82 | 0·700 |
| | 1·00 | 89 | 93 | 49 | 83 | 0·800 |
| | 2·50 | 89 | 105 | 37 | 76 | 1·000 |

may be caused partially by degradation products of DNA. A more detailed analysis of the acid-soluble fraction is now in progress.

These results are examples from a series of experiments under various conditions. Longer incubation of *E. coli B* cells with MC caused degradation of RNA and protein too. No degradation occurred when deoxyribonucleic acid from calf thymus and nucleic acid from herring sperm were incubated with MC *in vitro* under the same conditions as described here.

Takagi and Sekiguchi postulated that the inhibition of DNA formation in growing cells of *E. coli B* treated with MC is caused by an attack on synthesizing steps during DNA formation. However, they could not find any influence of MC on the polymerizing Kornberg enzyme. Furthermore, the block in DNA synthesis induced by MC was not overcome by the addition of thymine, thymidine or a mixture of deoxyribonucleotides to the medium.

The question arises: Is the inhibition of DNA formation in *E. coli B* treated with MC really caused by an attack in the synthesizing steps during DNA formation? The results presented here show that MC, under the experimental conditions described above, acts on the depolymerization of DNA*. If, in the presence of low levels of MC in the incubation medium of growing *E. coli B* cells, the synthesized DNA is partially degraded, the resulting picture is a block in DNA formation.

* *Note added in proof.* Tatum and co-workers obtained similar results (see ref. 7).

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## Ethanol Stimulation of Oxidative Metabolism in *Euglena gracilis*

*Euglena gracilis*, a flagellate protozoan, utilizes acetate and ethanol as energy and carbon sources. The acetate metabolism of *Euglena* grown on ethanol differs from that grown on acetate. Ethanol-grown cells have a rate of acetate oxidation at *p*H 7·0 lower than that of acetate-grown cells[1]. However, ethanol-grown cells incubated in the presence of acetate for about 80 min. often adapt to acetate, taking on characteristics similar to those of acetate-grown cells[1,2]. Thus, it was considered of interest to determine the respiration of *Euglena* in the presence of both acetate and ethanol.

Experimental and stock cultures of a streptomycin-bleached strain, *SM–LI*, of *Euglena gracilis* var. *bacillaris*, were grown axenically on the defined Cramer–Myers medium[3] with 0·061 *M* acetate as the sole carbon source for growth. The cells were gathered during the logarithmic growth phase, centrifuged twice in basal Cramer–Myers medium (minus acetate and vitamins $B_1$ and $B_{12}$), and re-suspended in a small volume of the basal medium. Cell concentrations ranged from $1·0 \times 10^8$ to $3·7 \times 10^8$ cells per flask. Absolute ethanol, in the amounts shown in Table 1, was added to Cramer–Myers medium which was then pipetted in 1-ml. quantities into the side-arms of the respiration flasks. The acetate concentration (0·061 *M*) was held constant in all experiments. Respiration-rates were determined by the direct method of Warburg[4]. After the substrate was tipped in, readings were taken at 10-min. intervals for 60 min. Respiration-rates were measured as $\mu l.\ O_2/10^8$ cells/hr. and are reported as per cent of the acetate control. All other conditions were as reported previously[5].

Table 1. Ethanol and Acetate Respiration* of Intact Acetate-grown *Euglena*

Average $Q_{O_2}$ for the acetate control (no ethanol) was 22·8 $\mu l.\ O_2/10^8$ cells/hr. Acetate concentration (0·061 *M*) was constant in all experiments. The control for each experiment was standardized at 100 per cent

| Ethanol molarity | No. of experiments | Average percentage of control |
|---|---|---|
| 0 | 5 | 100·0 |
| $6·83 \times 10^{-2}$ | 4 | 108·0 |
| $3·41 \times 10^{-2}$ | 3 | 112·0 |
| $1·71 \times 10^{-2}$ | 3 | 122·0 |
| $3·41 \times 10^{-3}$ | 5 | 129·0 |
| $6·83 \times 10^{-4}$ | 4 | 113·0 |
| $3·41 \times 10^{-4}$ | 4 | 102·0 |
| $1·71 \times 10^{-4}$ | 3 | 97·2 |
| $3·41 \times 10^{-5}$ | 3 | 97·5 |

* Gas phase, air; temperature, 26·5° C.

It is evident from Table 1 that the respiration of *Euglena* in the presence of acetate is stimulated by ethanol, a finding not reported before in the literature. The maximum effect of ethanol in these experiments occurs at a concentration of $3·41 \times 10^{-3}$ *M*. Higher and lower concentrations of ethanol result in a decreasing effect on the respiration of *Euglena*.

It appears that the ethanol may be affecting the cells by being oxidized within the cells to acetate, which in turn could enter the citric acid cycle or, perhaps, stimulate the formation of lipids. Bearing on this problem is a recent observation[6] which indicates that, in *Euglena* grown in the presence of both acetate and ethanol, more acetate carbon is assimilated into protoplasm than is oxidized as compared with cells grown in the presence of acetate alone. Although it has not been determined what substances are being formed in *Euglena* cells under these conditions, further work with labelled acetate and/or ethanol should help to explain these observations.

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## A Factor associated with 'Visking' Tubing capable of Antagonizing Insulin

During the investigation of the insulin antagonism associated with human serum albumin[1], 'Visking' tubing (Visking Corporation, Chicago, U.S.A.) was used for ultrafiltration and dialysis of protein solutions. The tubing itself has since been found to give rise to a substance which antagonizes insulin and which appears in the following circumstances:

Table 1. Effect of Dialysates and Ultrafiltrates from 'Visking' Tubing on the Glucose Uptake of Rat Diaphragms, with and without the Addition of Insulin to the Incubation Medium

| Buffer + insulin‡ | Dialysate or ultrafiltrate in buffer† + insulin‡ | Dialysate or ultrafiltrate in buffer† alone | Retentate in buffer† + insulin‡ |
|---|---|---|---|
| 16·58 ± 0·73 (10) | 5·33 ± 0·86 (11) | −2·3 ± 1·5 (8) | 715·80 ± 1·13 (3) |

Mean glucose uptake above basal-level* ± S.E. (mgm. glucose per 100 ml. per 10 mgm. diaphragm)

Number of experiments in parentheses.
* Amount of glucose taken up by the diaphragms when no insulin is added to the medium.
† Dialysates, ultrafiltrates and retentates were evaporated to dryness *in vacuo*, then dissolved in 9 ml. buffer for assay.
‡ Insulin added to make final concentration of 1,000 units/ml.

(1) When distilled water is ultrafiltered through 7-ft. of heavy grade 'Visking' tubing (27·32 in. inflated diameter) supported by 'Terylene' net, under a negative pressure of 40–50 cm. mercury, over a period of three days. (2) When 7 ft. light grade 'Visking' tubing (18·32 in.) is filled with water and suspended in changes of distilled water for 2–7 days, that is, used as dialysis tubing.

The ultrafiltrate or dialysate is evaporated to dryness *in vacuo*, and the residue when dissolved in buffer[2] is found to antagonize the action of insulin in the rat diaphragm assay system[3]. Under these conditions there is no significant reduction in the normal glucose uptake (Table 1, column 3). If the wider tubing is used as a true dialysing membrane, for example the removal of trichloracetic acid and ethanol, there is no trace of this antagonist in the retentate after dialysis (Table 1, column 4).

We attempted to extract the insulin inhibitor from the 'Visking' tubing before use to avoid interference with the true insulin antagonist associated with albumin, which is dialysable. Soaking for 6 days in cold water extracted relatively little of the antagonist, for subsequent dialysates or ultrafiltrates of distilled water through the treated tubing continued to inhibit insulin action. Continuous internal and external circulation of cold water for 3 days using the wider tubing gave a similar result (Table 2). It is seen that the wash was not always collected, since more importance was attached to the effects obtained from subsequent dialysis and ultrafiltration.

Table 2. Cold and Hot Water Washing of 'Visking' Tubing in an Attempt to Remove the Insulin Antagonist

| Experimental procedure | Buffer + insulin† | Wash + insulin† | Dialysate or ultrafiltrate + insulin† |
|---|---|---|---|
| | Mean glucose uptake above basal-level* ± S.E. (mgm. glucose per 100 ml. per 10 mgm. diaphragm) | | |
| Cold water for 6 days | | | |
| 18·32 in. 'Visking' | 17·15 ± 1·05 (2) | 3·2 (1) | 11·75 ± 0·25 (2) |
| 27·32 in. 'Visking' | 22·7 ± 0·0 (2) | 3·4 (1) | 18·05 ± 0·75 (2) |
| Continuous circulation of cold water for 3 days | | | |
| 27·32 in. 'Visking' | 14·7 (1) | — (—) | 7·95 ± 0·15 (2) |
| Water at 80° C. for 1 hr. | | | |
| 18·32 in. 'Visking' | 18·40 ± 0·43 (4) | 3·25 ± 1·50 (4) | 16·85 ± 0·74 (4) |
| 27·32 in. 'Visking' | 20·97 ± 0·15 (3) | — (—) | 11·7 ± 1·6 (2) |
| Boiling in water for 30 min. | | | |
| 27·32 in. 'Visking' | 14·62 ± 0·77 (5) | −1·95 ± 0·50 (4) | 12·58 ± 1·42 (4) |

Each horizontal line represents one complete series of experiments, the figures in parentheses indicating the total number of separate determinations for each series.
* Amount of glucose taken up by the diaphragms when no insulin is added to the medium.
† Dialysates, ultrafiltrates and retentates were evaporated to dryness *in vacuo*, then dissolved in 9 ml. buffer for assay.

Soaking the 'Visking' tubing in hot water for 1 hr. also gave rise to washes inhibiting insulin action. With the lighter grade of tubing (18·32 in.) no significant insulin antagonism could be detected afterwards in the dialysate. In contrast, the ultrafiltrate of the heavier grade tubing was only rendered completely free of the antagonist if the tubing were first boiled for 30 min. (Table 2). In this case, the concentration of antagonist in the wash was probably high, and there appeared to be some inhibition of the normal glucose uptake in addition to the inhibition of insulin action. No check was made for any change in porosity of the tubing which may have resulted from the boiling.

The antagonistic substance may well be a hydrolysis product of sulphur, since 'Visking' tubing is stated to contain up to 0·1 per cent sulphur, partially extracted by a hot aqueous wash (manufacturer's specifications). However, we do not intend to investigate this further, being more concerned with the isolation and characterization of the previously reported hormone-dependent insulin antagonist associated with plasma albumin[4].

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## Calcium and Magnesium Contents of Various Secretions entering the Digestive Tract of Sheep

The endogenous faecal excretion of calcium and magnesium is derived from the various digestive secretions and the desquamated epithelial cells of the alimentary tract. The relative proportions of these two fractions is unknown, but the fact that in calves[1] endogenous faecal excretion of magnesium increases during the first few weeks of life suggests that the contribution by the digestive juices is important. There is very little information on the calcium and magnesium content of the digestive secretions of ruminants beyond the values of 1·6–3·0 and 0·6–1·0 mgm./100 ml. for calcium and magnesium respectively in mixed saliva of sheep[2]. For this reason estimates of the probable quantities of these elements secreted into the alimentary tract of sheep were made. Calcium and magnesium were estimated in solutions of the ashed secretions.

The composition of the secretions collected from the various preparations is given in Table 1 and the daily output of calcium and magnesium as a result of these secretions has been assessed in Table 2 using representative volumes per 24 hr. of the various salivary secretions[2], gastric juice[4] and bile[5,6]. The range given for bile varied from 400 to 1,140 ml. per 24 hr., which may be accounted for by the fact that in some experiments collected bile was not returned to the duodenum. A daily volume of 1 litre was considered reasonable. Estimates of the daily secretion of pancreatic juice[5,7,8] vary from 275 to 600 ml., and a conservative value of 300 ml. was used in the with

Table 1. Calcium and Magnesium Content of Various Secretions from the Sheep's Digestive Tract

| Secretion | No. of animals examined | No. of samples analysed | Calcium* (m.equiv./l.) | Magnesium* (m.equiv./l.) |
|---|---|---|---|---|
| Parotid saliva | 9 | 12 | 0·74 (0·30–1·75) | 0·45 (0·17–1·32) |
| Submaxillary saliva | 8 | 10 | 1·88 (0·96–2·66) | 0·50 (0·10–1·00) |
| Residual saliva | 1 | 2 | 1·26 (1·12–1·40) | 1·36 (1·06–1·66) |
| Gastric juice | 2 | 45 | 1·68 (1·04–2·20) | 0·66 (0·52–0·88) |
| Bile | 3 | 30 | 4·56 (1·76–8·94) | 1·76 (0·50–3·90) |
| Pancreatic juice | 2 | 26 | 4·74 (3·96–5·82) | 1·13 (0·66–2·38) |
| Brünner's glands | 2 | 12 | 2·82 (2·56–3·18) | 0·90 (0·68–1·22) |
| Cæcum | 1 | 5 | 3·64 (2·24–5·66) | 2·53 (1·24–3·26) |
| Mixed secretions: Bile + pancreatic juice + Brünner's glands | 2 | 38 | 3·40 (1·08–6·32) | 1·48 (0·20–4·32) |
| Bile + pancreatic juice | 1 | 30 | 4·47 (3·60–5·84) | 1·12 (0·72–1·44) |

* Figures in parentheses denote maximum and minimum concentrations found.

given in Table 2. The volumes representing cæcal secretion and the secretions from Brünner's glands were obtained from the volumes collected from a cæcal pouch representing about half the whole organ (prepared by Dr. R. N. B. Kay) and from an isolated loop of duodenum which excluded the common opening of the bile and pancreatic ducts. The secretions of the cæcum have previously been estimated to amount to 180 ml. a day[5], a figure that is similar to the value given in Table 2. The calcium and magnesium contents of the secretions of the remainder of the small and large intestine were not estimated.

It has been calculated that a 40-kgm. sheep would contain respectively 16 and 28 m.equiv. of extracellular magnesium and calcium by assuming that the volumes of plasma and interstitial fluid represent 5 and 15 per cent of the body-weight respectively, and that the concentrations of calcium and magnesium in interstitial fluid are equivalent to the concentrations of ultrafilterable calcium and magnesium in plasma. These values are of the same order as the calculated amounts of these elements entering the digestive tract (Table 2). Calcium and magnesium secreted into the alimentary tract will be excreted in the fæces of the animal if they are not re-absorbed. It is interesting in this respect that the estimated total secretion of magnesium is of the same order as values reported in the literature for the daily endogenous fæcal magnesium in sheep, and as the contribution of magnesium by the secretion of the small intestine has been ignored, some re-absorption presumably occurs.

Table 2. Total Influx of Calcium and Magnesium in the Secretions of the Digestive Tract

| Secretion | Estimated daily volume* (litres) | Daily secretion of calcium (m.equiv.) | Daily secretion of magnesium (m.equiv.) |
|---|---|---|---|
| Parotid saliva | 5 | 3·70 | 2·25 |
| Submaxillary saliva | 0·5 | 0·94 | 0·25 |
| Residual saliva | 5 | 6·30 | 6·80 |
| Gastric juice | 5 | 8·40 | 3·85 |
| Bile | 1 | 4·56 | 1·76 |
| Pancreatic juice | 0·3 | 1·42 | 0·34 |
| Brünner's glands | 0·4 | 1·13 | 0·36 |
| Cæcum | 0·2 | 0·73 | 0·51 |
| Total | 17·4 | 27·18 | 16·12 |

* Figures arrived at from literature; for references, see text.

It would seem reasonable to assume that proportionately similar amounts of calcium and magnesium enter the bovine digestive tract. Analysis of two samples of parotid saliva revealed calcium and magnesium concentrations within the range of those found for sheep. Radioactive techniques have also demonstrated that circulating calcium is secreted into all parts of the bovine digestive tract, particularly the small intestine.

There is evidence that absorption from the digestive tract is an important factor contributing to the maintenance of magnesium concentrations in extracellular fluids of the adult ruminant, and magnesium balance studies on dairy cattle during their transfer from winter diets to diets of spring grass suggest that a reduced dietary intake of magnesium, coupled with a lower availability, is an important factor in the development of hypomagnesæmia[8]. The present investigations demonstrate that, should absorption of magnesium from the digestive tract be impeded, the continued secretion of magnesium in digestive juices would contribute to a rapid loss of extracellular magnesium.

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## Erythrocyte Glucose-6-Phosphate Dehydrogenase Deficiency in West Africa

Evidence is accumulating that sex-linked inherited deficiency of erythrocyte glucose-6-phosphate dehydrogenase is common in Central Africa. Frequencies of 15–30 per cent have been recorded in males living in malarious parts of the Belgian Congo[1], Nigeria[2] and East Africa[3]. In non-malarious parts of East Africa frequencies of 3 per cent or less have been found[3], and in South African Bantu the frequency is about 2 per cent[4].

The present investigation was undertaken in order to ascertain the distribution of this trait in West Africa. Males only were examined. Blood specimens were obtained from northern Nigerians through the courtesy of Dr. H. M. Archibald and Dr. C. G. Berry, Kano. The majority of subjects were Hausa, but small numbers of Fulani and other tribes were included. The samples from southern Ghana were obtained from two schools near Accra; 64 were Akim and the rest Ga.

Table 1. Frequency of Glucose-6-Phosphate Dehydrogenase Deficiency in West Africans

| Locality | No. tested | No. of enzyme deficient | Percentage of enzyme deficient |
|---|---|---|---|
| Northern Nigeria | 136 | 28 | 20·6 |
| Southern Ghana | 96 | 23 | 24·0 |
| Gambia | 103 | 16 | 15·5 |

The Gambian sample was taken from adult Mandinka living at Keneba in the West Kiang District of the Gambian Protectorate. Blood specimens were collected into acid-citrate-dextrose and sent in thermos flasks to London for testing. Glucose-6-phosphate dehydrogenase activity in erythrocytes was assayed by the technique of Motulsky. The results are shown in Table 1. All three groups showed enzyme deficiency, the frequency being highest in the sample from southern Ghana. These findings suggest that the enzyme-deficiency gene has a widespread distribution in West Africa. Tests on subjects such as the southern Liberians, who show low frequencies of haemoglobins *S* and *C*, would be of interest.

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## A New Technique of Chromatography and Ionophoresis on Ion-exchange Paper. Application to Separation of Compounds of Toxicological Interest: Separation of a Mixture of Promazine, Quinine, Sulphacetamide and Acetophenetidin

In two previous communications, we[1,2] have shown that a mixture of phenobarbitone, acetophenetidin, salicylate and *p*-acetylaminophenol can be separated in 60–75 min. by a combined technique of chromatography and ionophoresis on Whatman ion-exchange cellulose papers. We have now been able to effect the resolution of a mixture of basic and neutral drugs, namely, promazine, quinine, sulphacetamide and acetophenetidin.

This separation was achieved by applying solutions of these drugs to a sheet of diethylaminoethylcellulose paper and carrying out chromatography in a 0·1 *M* solution of the disodium salt of ethylenediaminetetraacetic acid for 20 min. At the end of this period the wet sheet was subjected to ionophoresis at a constant current of 10 m.amp. for 30 min. Both the chromatography and the ionophoresis were carried out in the same tank as described previously[1,2].

Fig. 1 shows the results of this experiment, from which it is seen that chromatography effects a separation into three parts, namely, promazine, quinine and a mixture of sulphacetamide and acetophenetidin. The sulphacetamide and acetophenetidin are quite

Fig. 1. Chromatography in 0·1 *M* ethylenediaminetetraacetic acid (20 min.) followed by ionophoresis in 0·1 *M* ethylenediaminetetraacetic acid (30 min., 10 m.amp.) of a mixture of promazine (*A*), quinine (*B*), acetophenetidin (*C*) and sulphacetamide (*D*). Mixture applied at point marked *P*. Arrow indicates direction of ascending solvent flow during chromatography

clearly separated by ionophoresis. Examination of the wet paper in 254 mμ light shows promazine as a blue fluorescent spot, sulphacetamide as a light-blue absorbing spot and acetophenetidin as a dark-purple absorbing spot. Quinine is not visible on the wet paper. After drying the paper, which takes 3–4 min. with a hair-dryer, the promazine shows up as a brilliant yellow fluorescent spot. Quinine can be revealed as a bright blue fluorescent area by holding the paper over the mouth of a bottle of concentrated hydrochloric acid. The other two compounds show the same absorption colour as on wet paper.

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## Detection of Small Quantities of 3,4-Benzpyrene directly from Chromatographic Paper

W. Davies and J. R. Wilmshurst recently published a report[1] on the detection of 3,4-benzpyrene, under the most favourable conditions, in a concentration of $10^{-8}$ gm./ml., using fluorescent spectrography (Hilger medium spectrograph).

We detected 3,4-benzpyrene directly from chromatographic paper in a quantity of $10^{-9}$ gm. on the chromatographic spot 60–90 mm.[2] in size. This was done by means of fluorescent spectrography (Hilger medium spectrograph, quartz optics). Actually we applied this procedure for detecting carcinogenic substances from mixtures of organic compounds as follows: an extract of coal soot, previously chromatographed on an alumina and silica column, was transferred to chromatographic acetylated paper[2] (Whatman No. 1). The spots developed on the chromatogram and which showed fluorescence were set directly facing the spectrograph slit and were illuminated with Wood's light (Quarzlampen, Hanau S., 300 *PL* 12; 220 V.; 2·5 amp., with Wood's glass filter). From one of the spectrographed spots we obtained the characteristic band spectrum of 3,4-benzpyrene.

This method, a combination of paper chromatography and fluorescent spectrography, facilitates greatly the detection of minute quantities of 3,4-benzpyrene and other fluorescent substances with a characteristic band spectrum, as in this way it is possible to avoid elution and subjecting the solution to spectrographic analysis.

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## PHYSIOLOGY

### Effect of Feeding Two Levels of Dietary Calcium on the Growth of Broiler Chickens

The dietary requirements of calcium for chickens 0–18 weeks of age has been stated by the U.S. National Research Council[1] to be 1·0 per cent of the diet. In the United Kingdom commercial broiler rations contain at least 1·0 per cent but may contain up to 1·4 per cent. Davis[2] has presented evidence taken mainly from laboratory animal experiments indicating that the utilization of dietary protein, fat, minerals, and vitamins may be reduced appreciably when the dietary calcium level exceeds 1·0 per cent. When there is a limited intake of these nutrients, the inclusion of a high level of calcium in the diet may result in a clinical deficiency of them.

During the course of a large-scale experiment conducted by us it was possible to compare the effect of a diet containing approximately 0·8 per cent calcium with that of a diet containing approximately 1·3 per cent calcium on the rate and efficiency of gain of broiler chickens from one day to ten weeks of age. The results of this experiment provide further evidence that the efficiency of utilization of nutrients may be affected by the level of dietary calcium.

The experiment was conducted during March–May 1960 in a commercial-type broiler house designed to accommodate thirty pens, each housing one hundred and fifteen chickens from day old to ten weeks of age. Fifteen pens were allocated at random to a commercial broiler ration containing 1·35 per cent calcium, and the other fifteen pens of chickens were fed the same commercial ration with 0·83 per cent calcium. The latter ration was prepared by excluding calcium carbonate which normally was included to bring the level of calcium up to 1·0 per cent and above. The average levels of protein, calcium and phosphorus determined from five samples of each of the two rations are given in Table 1.

The average gain in live-weight, the average food consumption, and the average food conversion efficiency observed for the first six weeks and for the total ten weeks of the experiment are presented in Table 2. The birds fed the 0·83 per cent calcium diet grew 3·4 per cent faster up to six weeks and also up to ten weeks of age than the birds fed the 1·35 per cent calcium diet. These increases in gain were highly significant ($P<0·001$). Over the first six weeks there was no significant difference in food consumption, but over the total ten-week period the birds on the 0·83 per cent calcium diet consumed 2·7 per cent less food than the birds fed the 1·3 per cent calcium diet. This result was highly significant ($P<0·001$).

Table 1. Levels of Crude Protein, Calcium and Phosphorus in Rations

| Ration | Crude protein (per cent) | Calcium (per cent) | Phosphorus (per cent) |
|---|---|---|---|
| 0·8 per cent calcium | 24·38 ± 0·49* | 0·83 ± 0·08 | 0·52 ± 0·02 |
| 1·3 per cent calcium | 23·63 ± 0·55 | 1·35 ± 0·11 | 0·53 ± 0·01 |

* S.D.

Table 2. Average Live-weight Gain, Food Consumption and Food Conversion Efficiency to Six Weeks and Ten Weeks of Age

| Ration | Average gain (lb.) | Average food consumed (lb.) | Average food consumed lb. live-weight gain (lb.) |
|---|---|---|---|
| | 0–6 weeks | | |
| 0·8 per cent calcium | 1·784* | 3·606 | 2·022* |
| 1·3 per cent calcium | 1·725 | 3·601 | 2·087 |
| S.E. of difference | ± 0·014 | ± 0·047 | ± 0·017 |
| | 0–10 weeks | | |
| 0·8 per cent calcium | 3·702* | 9·334* | 2·522* |
| 1·3 per cent calcium | 3·580 | 9·593 | 2·680 |
| S.E. of difference | ± 0·026 | ± 0·070 | ± 0·012 |

* $P < 0·001$

Over the six-week and ten-week stages, respectively, the birds fed the 0·83 per cent calcium diet converted their food 3·1 and 5·9 per cent more efficiently than the birds fed the 1·3 per cent calcium diet. Again these results were highly significant ($P<0·001$).

The birds were slaughtered at ten weeks of age, and the resulting carcases were graded according to normal commercial standards. The resulting data are presented in Table 3. There was no significant difference in the percentage of grade *A* or grade *B* carcases from the two experimental groups. However, the average carcase weight of birds fed the 0·83 per cent calcium diet was 3·9 per cent higher than that of the birds fed the 1·35 per cent calcium diet. This highly significant difference ($P<0·001$) resulted wholly from the increased weight of grade *A* carcases, since the weight of grade *B* carcases was not significantly affected.

Table 3. Carcase Quality Data

| | 0·8 per cent calcium diet | 1·3 per cent calcium diet | S.E. of difference |
|---|---|---|---|
| Percentage of 'Grade *A*' carcases | 78·0 | 82·4 | ± 2·29 |
| Percentage of 'Grade *B*' carcases | 22·0 | 17·6 | ± 2·29 |
| Average weight of all carcases (lb.) | 3·23* | 3·11 | ± 0·02 |
| Average weight of 'Grade *A*' carcases (lb.) | 3·18* | 3·06 | ± 0·02 |
| Average weight of 'Grade *B*' carcases (lb.) | 3·33 | 3·38 | ± 0·07 |

* $P < 0·001$.

It should be noted that although the 0·83 per cent calcium diet averaged 0·75 per cent more protein than the 1·35 per cent calcium diet, it is unlikely that this extra protein would have produced the effects which we have attributed to the differences in level of calcium.

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## Replacement of Adrenaline and Noradrenaline in the Adrenal Gland of the Rat, following Depletion and Redepletion with Reserpine

In a previous communication[1], we showed that reserpine causes a similar percentage loss of adrenaline and noradrenaline from the adrenal glands of the rat. Recovery of the catechol amines was slow, the amine content returning to normal within 21 days. The adrenaline content gradually returned to the control value, whereas the noradrenaline content first increased rapidly to a level well above normal at 7 days before falling to the control value.

To determine whether or not the recently replaced amines are bound in the medullary cells in a different manner from the amines that are not released during depletion, it was decided to redeplete the glands at 7 and 21 days. Redepletion at 7 days would detect any difference in the sensitivity to reserpine of the recently replaced amines and redepletion at 21 days would reveal whether or not the glands had, at that time, returned to normal with respect to their sensitivity to further reserpine treatment.

In this series of experiments groups of 5 male albino rats weighing 150–190 gm. were used. The treatment they received and the schedule of killing are shown in Table 1. Four 7-day and two 21-day redepletion experiments were performed. In all 88 groups of 5 rats were used. Each test group had its own control group also of 5 rats. In every instance except the 10-day point in the 7-day redepletion experiments, the control groups consisted of glands from rats given the reserpine solvent only. The control group for the 10 day point was obtained from the glands of rats given reserpine on days 0, 1 and 2 and killed on day 10 (Table 1). This represents the amine content that the redepleted group would have attained if it had not been further treated with reserpine. Subsequent to this 10-day point the controls were the normal solvent-injected rats, because it was found that the relative amounts of adrenaline and noradrenaline following redepletion were very similar to the amounts following the initial depletion. The glands were extracted with N/10 hydrochloric acid and assayed biologically as described previously[1].

As can be seen from Fig. 1, redepletion at 7 days caused a preferential loss of noradrenaline, the newly replaced amine thus appearing more susceptible to the action of reserpine than that remaining after the initial depletion. The subsequent recovery of the noradrenaline content was similar to the initial recovery, with a peak of noradrenaline occurring 7 days after the beginning of redepletion. The noradrenaline content was still slightly raised above the control-level at 21 days. The replacement of adrenaline was similar to that which occurred in the initial depletion experiments.

Table 1

| Group | Day: Reserpine (1 mgm./kgm. subcutaneously) administered | | | | | | Killed |
|---|---|---|---|---|---|---|---|
| Depletion | 0 | 1 | 2 | | | | 3 |
| | 0 | 1 | 2 | | | | 7 |
| | 0 | 1 | 2 | | | | 14 |
| | 0 | 1 | 2 | | | | 21 |
| 7-day redepletion | 0 | 1 | 2 | 7 | 8 | 9 | 10 |
| | 0 | 1 | 2 | 7 | 8 | 9 | 14 |
| | 0 | 1 | 2 | 7 | 8 | 9 | 21 |
| | 0 | 1 | 2 | 7 | 8 | 9 | 28 |
| 21-day redepletion | 0 | 1 | 2 | 21 | 22 | 23 | 24 |
| | 0 | 1 | 2 | 21 | 22 | 23 | 28 |
| | 0 | 1 | 2 | 21 | 22 | 23 | 35 |
| | 0 | 1 | 2 | 21 | 22 | 23 | 42 |

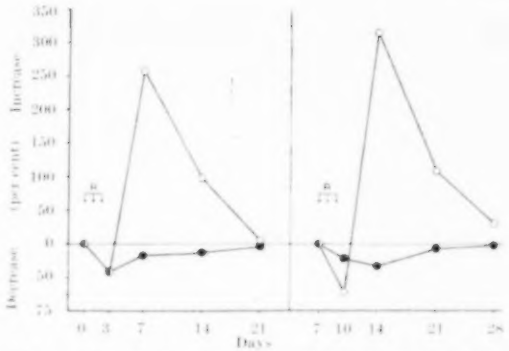


Fig. 1. Effect of redepletion with reserpine, at 7 days, on the adrenaline (●) and noradrenaline (○) content of rat adrenal glands. Left, depletion; right, redepletion

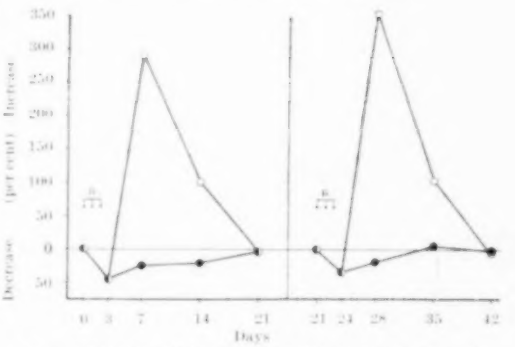


Fig. 2. Effect of redepletion with reserpine, at 21 days, on the adrenaline (●) and the noradrenaline (○) content of rat adrenal glands. Left, depletion; right, redepletion

Redepletion at 21 days (Fig. 2) caused losses of both adrenaline and noradrenaline similar to those which had occurred in the initial depletion experiments. The recovery of both amines was similar to that obtained initially with a peak of noradrenaline occurring at 28 days, that is, at 7 days following the beginning of redepletion.

Thus it appears that at 21 days the rat adrenal gland has recovered its normal catechol amine content following a 50 per cent loss produced by reserpine. However, the preferential loss of noradrenaline occurring when redepletion occurred at 7 days resulted in the noradrenaline content of the glands being depleted to the same absolute amount as that following the initial depletion. Thus it seems possible that, under the experimental conditions described here, it is the newly synthesized noradrenaline that is released before there is time for it to be converted to adrenaline.

We wish to thank Ciba Laboratories, Ltd., for generous gifts of reserpine.

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## Choline Acetylase in the Human Placenta at Different Stages of Development

It has long been known that there is acetylcholine in the human placenta[1] and Comline's[2] experiments established that choline acetylase, the enzyme which synthesizes acetylcholine, is in the placenta as well. The rate of acetylcholine synthesis, which he observed in extracts of acetone powders, made from mature placentæ, was between 0·6 and 0·75 mgm./gm. acetone-dried tissue/hr. Later in this laboratory, when a coupled enzyme system was used to provide an independent supply of the substrate acetyl-co-enzyme *A*, rates of 5–6 mgm./gm./hr. were obtained[3].

More recently we have re-measured the choline acetylase activity in mature and in some early placentæ (at 15, 24, 25 and 34 weeks of development) and have found that the choline acetylase activity of the early placentæ is higher than of those which reach term. But the activity even in the fully developed placentæ may be much greater than that reported earlier. Expressed (in terms of the chloride) as the amount of acetylcholine produced per gm. acetone powder, per hr., rates as high as 34 mgm. have been observed. Neither the fœtal blood nor the other fœtal membranes (amnion, umbilical cord) have any significant activity and the placental tissue washed free of blood is found to synthesize acetylcholine at the same or little higher rate than samples that contain blood. In this respect the enzyme differs from placental cholinesterase, since it appears from Ord and Thompson[4] that cholinesterase of the placental tissue and of the blood which it contains is about equal.

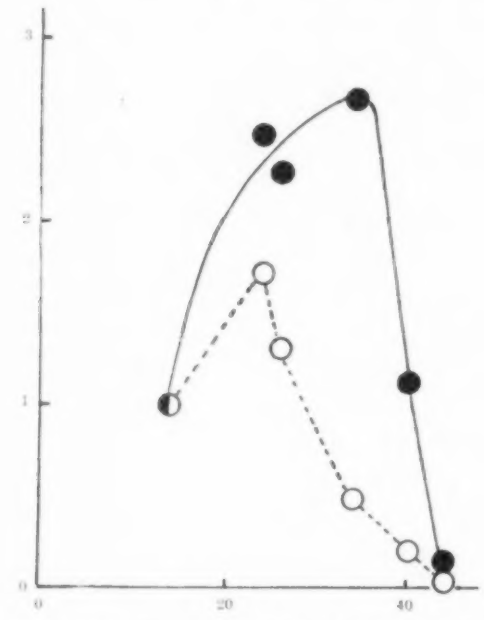


Fig. 1. Choline acetylase activity of the human placenta at different stages of development. The activity is determined by measuring the amount of acetylcholine produced by incubating an extract of a known quantity of tissue (equivalent to 1 mgm. or more) for 1 hr. at 38·5° C. in a system containing coenzyme *A*, acetylphosphate, phosphotransacetylase, choline, *l*-cysteine, potassium chloride, magnesium chloride, eserine sulphate and sodium phosphate buffer (*p*H 6·9). The ordinate is the amount of acetylcholine expressed as gm. acetylcholine-chloride and the abscissa is the developmental age of the placenta in weeks. ○, activity per 100 gm. of tissue; ●, activity per total weight of organ

By comparison with the mature placentæ those in which development had been interrupted at an early stage had extraordinarily high concentrations of choline acetylase. The highest activity was exhibited by a placenta thought to be 24 weeks old. Acetone powders made from this specimen had an average activity of 130 mgm. acetylcholine-chloride/gm./hr., equivalent to 17·1 mgm./gm. fresh tissue and a total activity for the whole organ of about 2·0 gm./hr. The specific activity of the extracts, or the amount of acetylcholine formed per mgm. of protein was 7·6 $\mu M$. So far as we are aware, this is the highest activity yet reported for any vertebrate tissue.

Fig. 1 shows how both concentration and total activity vary during development of the placenta. Although, as already mentioned, the concentration was highest at 24 weeks, the total amount was higher in the 34-week placenta. This suggests that the tissue containing the enzyme continues to grow for the first 24–34 weeks; but that some time before 34 weeks its growth is overtaken by the growth of other tissue elements with the consequence that its concentration falls. At the end of pregnancy, however, there is a decrease both in concentration and total amount of choline acetylase. This might be due either to involution and degeneration of the tissue containing the enzyme, or its denaturation. We have some evidence to suggest that this might occur by oxidation of its sulphydryl groups.

The results are of interest in that they strengthen the view that acetylcholine is of importance in placental function during pregnancy. Present indications are that the enzyme is located in the chorionic villi, in the cell layers separating maternal from fœtal blood. We are tempted to suggest therefore that its function is in the active transport of materials across this barrier.

We are grateful to Dr. J. Dickie at the County Maternity Hospital, Cambridge, for enabling us to obtain the placentæ and providing the clinical history of each.

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## Effect of Dimethyl Sulphoxide on the Cryo-tolerance of Mitochondria

The integrated structural and functional complexes of many biological entities have been conserved by freezing and storage at low temperatures. The cryo-tolerance of enzymes, viruses, bacteria, cells or tissues has been increased by the inclusion of 'protective substances' in the suspending medium[1,2]. We have reported recently the role of glycerol in protecting oxidative phosphorylation by suspensions of mitochondria during freezing or freezing and storage at low temperatures[3]. Dr. Audrey Smith, of the National Institute for Medical Research, London, suggested to

us that dimethyl sulphoxide could replace glycerol. Our preliminary work has shown dimethyl sulphoxide to be equal to glycerol as a protective substance and to be superior in certain instances.

Suspensions of mitochondria were prepared from the livers of Sprague-Dawley rats. Two procedures were used: (1) mitochondria were prepared in isotonic sucrose containing dimethyl sulphoxide; (2) the total isolation of mitochondria was carried out in isotonic sucrose and dimethyl sulphoxide was added to the final suspension. Both preparations contained $3 \cdot 5 \times 10^{-3}$ *M* versene. All preparative steps were at 0–2°. Oxidative phosphorylation, using α-ketoglutarate as substrate, was measured by a modification[4] of the method of Lardy and Wellman[5]. Aliquots of suspensions of mitochondria, 0·8 ml., were placed in tubes and frozen slowly by immersion into −76° baths, 'dry ice' and acetone, with continuous swirling to distribute the mitochondria evenly on the sides of the tubes. Frozen suspensions were thawed by placing the tubes at 30° until melting was initiated; the samples were then kept in an ice-bath until used.

Because of the intimate contact between mitochondrial elements and the substance to be tested, the several concentrations of dimethyl sulphoxide were tested first by procedure 1. The concentrations of dimethyl sulphoxide of those preparations showing the best overall retention of oxidative phosphorylation after freezing or freezing and storage at low temperatures were tested further by procedure 2. The results of these investigations are shown in Table 1. Differences of 3 μmoles in the esterification of inorganic phosphate or 2 μatoms in the uptake of oxygen were statistically significant[3].

In procedure 1, oxidative phosphorylation was not affected in suspensions of mitochondria prepared in isotonic sucrose containing 5 or 10 per cent dimethyl sulphoxide. Phosphorylation was significantly lower in suspensions prepared in 20 per cent dimethyl sulphoxide; oxidation was not altered. Concentrations of 30 per cent were toxic. A significant decrease in oxidative phosphorylation was observed in suspensions containing 5 per cent dimethyl sulphoxide and frozen slowly at −76°; the decrease in phosphorylation was greater than that of the control frozen similarly. Freezing did not alter further oxidative phosphorylation by suspensions containing 10 and 20 per cent dimethyl sulphoxide. Phosphorylation was significantly less in all groups after storage at −65° for 18 days, averaging 11·7 per cent in relation to the values of frozen suspensions; oxidation was unchanged in groups exposed to 10 or 20 per cent dimethyl sulphoxide and significantly lower in the 5 per cent group.

In procedure 2, the values for oxidative phosphorylation by non-frozen, frozen or frozen and stored suspensions of mitochondria isolated in isotonic sucrose prior to the addition of dimethyl sulphoxide, in amount to give a 10 per cent solution, were not significantly different from that of the non-frozen control. Oxidative phosphorylation by non-frozen suspensions of mitochondria containing 20 per cent dimethyl sulphoxide was not different from the non-frozen control. The oxidative and phosphorylative capacities of the suspensions above following freezing or freezing and storage were not different from those suspensions containing 20 per cent dimethyl sulphoxide and prepared by the first procedure.

Neither 5 nor 10 per cent dimethyl sulphoxide nor glycerol affected adversely oxidative phosphorylation by suspensions of mitochondria (all references to glycerol are based on data in ref. 3). The losses in phosphorylation by suspensions of mitochondria prepared with 20 per cent dimethyl sulphoxide (procedure 1), were approximately one-half those observed when 20 per cent glycerol was used, being 16 and 32 per cent respectively; oxidation was affected similarly. No losses were found in oxidative phosphorylation by suspensions containing 20 per cent dimethyl sulphoxide. Suspensions prepared by procedure 2, and containing 20 per cent glycerol, on the other hand, lost approximately 25 per cent of their ability to carry out oxidative phosphorylation. Mitochondria exposed to 30 per cent glycerol (procedure 1), were inactivated; suspensions exposed to 30 per cent dimethyl sulphoxide retained their capacity for oxidative phosphorylation, but at a greatly reduced level. These results indicate that dimethyl sulphoxide is less toxic to mitochondria than glycerol.

Both 10 per cent dimethyl sulphoxide and glycerol protected fully oxidative phosphorylation by suspensions of mitochondria frozen slowly at −76°. In the case of the former, both procedures were equally effective; the latter, on the other hand, was effective fully only with procedure 1. At a diminished concentration (5 per cent), procedure 1, greater protection was observed with dimethyl sulphoxide. Thus, with comparable concentrations and techniques of application, dimethyl sulphoxide was equal or superior to

Table 1. Effects of Several Concentrations of Dimethyl Sulphoxide on Oxidative Phosphorylation by Suspensions of Mitochondria Frozen Slowly at −76° or Frozen Slowly at −76° and Stored at −65° for 18 Days

| Dimethyl sulphoxide (per cent) | Treatment | Procedure 1* P (μmoles) | Procedure 1* O (μatoms) | Procedure 1* P : O | Procedure 2† P (μmoles) | Procedure 2† O (μatoms) | Procedure 2† P : O |
|---|---|---|---|---|---|---|---|
| 0 (control) | Non-frozen | 35·48 | 11·61 | 3·06 | | | |
| | Frozen | 29·95 | 10·77 | 2·78 | | | |
| | Stored | 28·24 | 10·17 | 2·58 | | | |
| 5 | Non-frozen | 33·60 | 10·44 | 3·22 | | | |
| | Frozen | 25·79 | 8·13 | 3·17 | | | |
| | Stored | 22·63 | 6·47 | 3·65 | | | |
| 10 | Non-frozen | 35·59 | 10·40 | 3·42 | 36·83 | 11·24 | 3·28 |
| | Frozen | 36·86 | 10·64 | 3·46 | 35·59 | 11·00 | 3·24 |
| | Stored | 31·67 | 9·84 | 3·22 | 36·23 | 11·71 | 3·09 |
| 20 | Non-frozen | 29·54 | 10·49 | 2·82 | 34·18 | 11·15 | 3·07 |
| | Frozen | 30·78 | 10·56 | 2·91 | 30·26 | 10·16 | 2·98 |
| | Stored | 27·68 | 10·53 | 2·63 | 29·78 | 10·18 | 2·93 |
| 30 | Non-frozen | 10·40 | 4·83 | 2·15 | | | |
| | Frozen | 0·00 | 0·00 | | | | |

* Mitochondria prepared in isotonic sucrose containing dimethyl sulphoxide.
† Dimethyl sulphoxide added to isolated mitochondria suspended in isotonic sucrose.

glycerol for protecting the oxidative and phosphorylative capacities of suspensions of mitochondria following freezing.

No losses in oxidative phosphorylation were found when 10 per cent glycerol (procedure 1), or 10 per cent dimethyl sulphoxide (procedure 2) were used to protect mitochondria during storage at −65° for 15 and 18 days respectively, the only comparison possible at present. However, procedure 2 is allied more closely than procedure 1 to the methods of preserving biological materials, that is, putting cells and tissues in solutions containing the protective substance prior to freezing and storage. Therefore, it is likely that dimethyl sulphoxide, by protecting mitochondrial elements with greater efficiency than gly .ol, will be found to protect cells more effectively than glycerol from freezing and storage at low temperatures.

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## Preservation of Mouse Bone Marrow at −79 C. with Dimethyl Sulphoxide

Dimethyl sulphoxide was used by Lovelock and Bishop[1] to protect bovine erythrocytes against the damaging effects of freezing to, and thawing from, low temperatures. The bovine erythrocyte is impermeable to glycerol, which does not protect it from the damage caused by freezing. Dimethyl sulphoxide has recently been shown to protect mouse bone marrow from the damaging effects of freezing to −79° C. (ref. 2). After thawing, the protected cells retained between 50 and 60 per cent of their ability to synthesize lipids and proteins. Fluorescence microscopy with acridine orange revealed the presence of many intact erythroid and myeloid cells. It has now been demonstrated that mouse bone marrow stored for one month at −79° C. in the presence of dimethyl sulphoxide will prevent the death of lethally irradiated mice.

Bone marrow cells were obtained from the femora of 12-week old female mice of an inbred *CBA* strain. The cells were suspended in Parker '199' tissue culture fluid containing 33 per cent rat serum and 15 per cent (v/v) dimethyl sulphoxide. Ampoules containing 50 × $10^6$ nucleated cells in 1 ml. were cooled slowly to −79° C. in the apparatus described by Polge and Lovelock[3]. Marrow cells were also frozen in the absence of dimethyl sulphoxide. After one month at −79° C., ampoules were thawed rapidly at +37° C. and the bone marrow cells injected intravenously into lethally irradiated mice.

Table 1. Survival of Lethally Irradiated Mice injected with Isologous Marrow preserved at −79° C. for one month with Dimethyl Sulphoxide

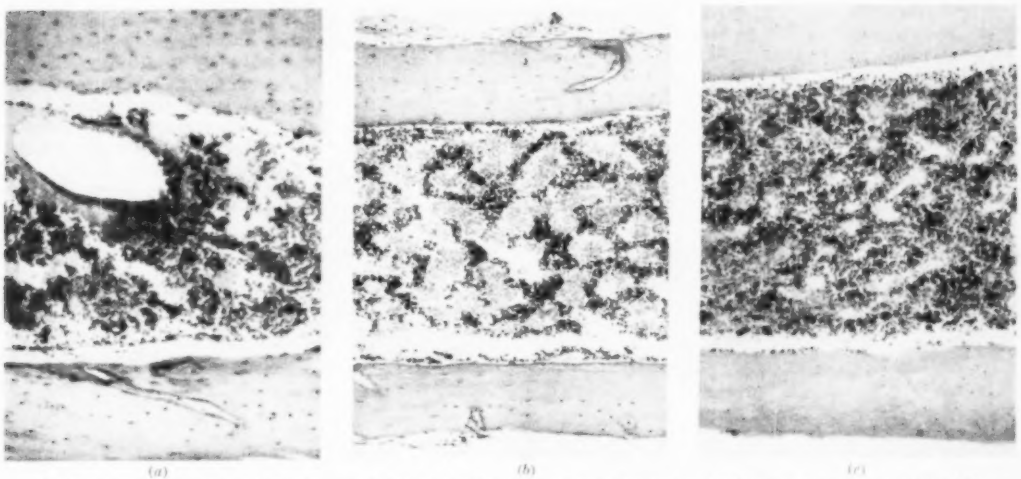
| Treatment (No. of nucleated cells) | No. of mice | No. living at 30 days | Survival (per cent) |
|---|---|---|---|
| Controls, injected with Parker/serum/dimethyl sulphoxide medium (0·5 ml.) | 19 | 0 | 0 |
| Fresh marrow; 5 × $10^6$ in 0·5 ml. of Parker/serum/sulphoxide | 18 | 15 | 83 |
| Marrow frozen without dimethyl sulphoxide; 5 × $10^6$ in 0·5 ml. of Parker/serum | 26 | 2 | 7·7 |
| Marrow frozen in the presence of 15 per cent dimethyl sulphoxide; 5 × $10^6$ in 0·5 ml. of Parker/serum/sulphoxide | 27 | 19 | 70 |

Female *CBA* mice of the same strain and age as the donor animals were irradiated with 1,000 r. of X-rays ($LD_{99}$ at 30 days). The X-ray apparatus used was a Newton Victor *G* × 10 operated with the following factors: 120 kV.; 5·5 m.amp.; 1 mm. aluminium filter; dose-rate of 48 r. per min. Immediately after irradiation, the mice were allocated at random to four groups. One group received 5 × $10^6$ fresh marrow cells; a second group received 5 × $10^6$ cells which had been preserved at −79° C. for one month with dimethyl sulphoxide; the third group was injected with the same number of cells frozen for one month without dimethyl sulphoxide, and the last group was injected with Parker-serum-sulphoxide medium only. The number of mice alive 30 days post-radiation in the four treatment groups is shown in Table 1. These results indicate that marrow preserved by dimethyl sulphoxide at −79° C. is only slightly inferior to fresh marrow in preventing radiation death.

A second experiment was designed to study the haematological response of lethally irradiated mice to fresh marrow and preserved marrow. Mice were killed at intervals following the injection of different numbers of fresh cells and a standard dose of frozen cells preserved in dimethyl sulphoxide. Re-population of the marrow cavity of the femur was evident on the eighth day after irradiation in the group of mice which received the marrow frozen in the presence of sulphoxide (see Fig. 1). By the twelfth day the cellularity of the marrow was almost normal, and cells of all types, including megakaryocytes, were present. Mice which had been injected with the same number (5 × $10^6$) of fresh marrow cells showed evidence of re-population of the femur between the sixth and seventh day. The femora of mice which had received marrow frozen in the absence of dimethyl sulphoxide and of those which had been injected with cell-free medium showed no signs of re-population and most of these animals were dead by the tenth day.

Leucocyte counts on the peripheral blood from these animals and of others which had been injected with smaller doses of fresh bone marrow are shown in Fig. 2. The leucocyte response of mice which had received frozen marrow preserved with dimethyl sulphoxide was slightly better than the response obtained with 1 × $10^6$ fresh cells. This implies that more than 20 per cent of the myeloid stem cells in the frozen marrow sample were viable.

Blood leucocyte-levels were normal (greater than 9,000 per c.mm.) within 14 days in those mice treated with 5 × $10^6$ fresh cells and within 17–18 days in mice treated with the same number of cells frozen in the presence of sulphoxide. In both cases, however, the



(a) (b) (c)

Fig. 1. Femora of X-irradiated mice (haematoxylin and eosin). (a) Untreated control 8 days after X-irradiation. (× 85); (b) treated with bone marrow stored at − 79° C.; 8 days after X-irradiation (× 67); (c) treated with bone marrow stored at −79° C.; 12 days after X-irradiation (× 75)

differential counts were abnormal. Nearly 75 per cent of the leucocytes were polymorphs and only 25 per cent were lymphocytes and monocytes. This is almost a quantitative reversal of the normal differential blood picture.

Work is in progress to compare the haematological response of lethally irradiated mice with marrow preserved with glycerol and dimethyl sulphoxide.

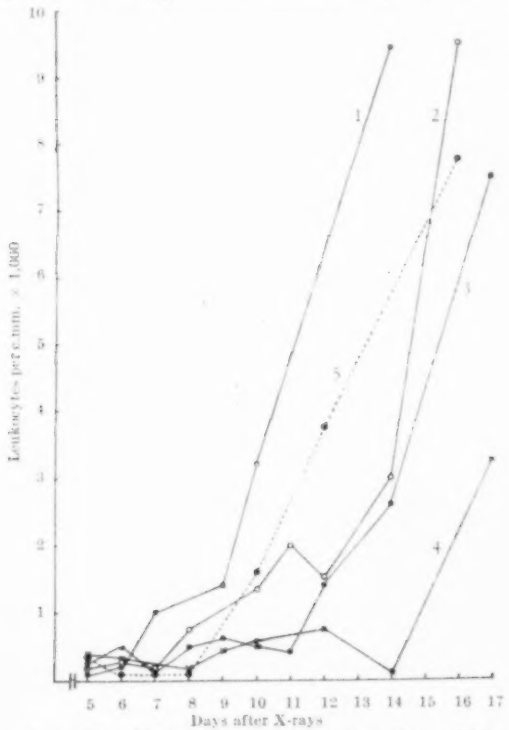



Fig. 2. Effect of fresh marrow and marrow preserved at − 79° C. with dimethyl sulphoxide on the recovery of blood leucocytes in lethally irradiated mice. (1) 5 × $10^8$ cells; (2) 1 × $10^8$ cells; (3) 0·5 × $10^8$ cells; (4) 0·1 × $10^8$ cells; (5) 5 × $10^8$ frozen cells

I wish to thank Dr. A. U. Smith for useful suggestions.

*Note added in proof.* Since this work was completed, comparisons with marrow preserved with dimethyl sulphoxide and with 15 per cent glycerol have indicated the superiority of dimethyl sulphoxide as a low-temperature preservative agent. The number of animals which survived lethal X-irradiation when treated with either marrow preserved with glycerol or sulphoxide was about the same. The onset of reticulocytosis and the start of the leucocyte response, however, occurred about two days later in mice injected with 5 × $10^8$ cells which had been kept for one month at −79° C. in the presence of 15 per cent glycerol.

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## Role of the Mucous Membrane in the Peristaltic Reflex in the Isolated Ileum of the Guinea Pig

Bülbring, Lin and Schofield[1] have presented evidence which suggested that receptors of the sensory neurones subserving the peristaltic reflex in the isolated small intestine of the guinea pig, rabbit and cat are present in the mucous membrane. Ginzel[2], on the other hand, showed that necrosis of the mucous membrane brought about by 30 per cent silver nitrate or 20 per cent tannic acid did not abolish the peristaltic reflex. He concluded that mucosal nerve fibres were not essential for this reflex.

When the peristaltic reflex is investigated by the technique of Trendelenburg[3], the fluid which distends the lumen and is then ejected by the peristaltic movement is not renewed during the experiment; thus any material which may be shed by the mucous membrane will accumulate in this fluid. If the preparation is left in the organ bath for some hours and the peristaltic reflex elicited at intervals, it may

be noted that the fluid ejected from the lumen becomes increasingly turbid, and at the same time the intestinal wall appears more and more transparent. This suggested to us that a part of the mucous membrane is lost while the ileum is in the organ bath.

This possibility was tested in a series of experiments in which pieces of ileum were left in the organ bath for varying periods, during which the peristaltic reflex was elicited every 30 min. At the end of the experimental period the gut was fixed for histological examination.

Changes in the villi occurred as early as 30 min. after setting up the preparation and consisted of a swelling of the stroma of the villi, particularly at their tips (Fig. 1, *B*); at this stage most of the epithelial cells were still in place although they showed degenerative changes. Half an hour later (Fig. 1, *C*), the swollen distal ends of the villi had been shed into the lumen, where chains of epithelial cells were found. In the course of the next few hours more and more of the mucous membrane was lost until, after 18 hr., very little live mucosal tissue was left (Fig. 1, *D*–*F*). No obvious changes were observed in the muscle fibres.

The segments of the ileum from which the sections shown in Fig. 1, *B*–*E* were obtained, that is up to 8 hr. after setting up the preparation, still exhibited a normal peristaltic reflex. In the ileum which, after 18 hr. in the organ bath, had the histological appearance of Fig. 1, *F*, distension of the lumen elicited a reflex as late as 16 hr. after setting up the preparation. From these experiments it may be concluded that, if stretch receptors subserving the peristaltic reflex are present in the mucous membrane, they are situated in its basal layers.

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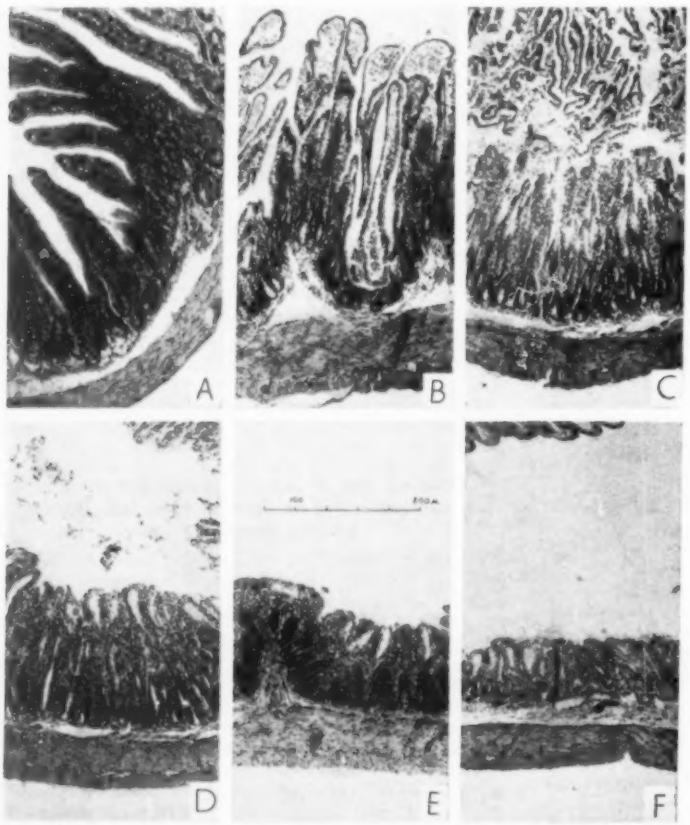


Fig. 1. The histological appearance of the isolated ileum of the guinea pig at intervals after setting up in an organ bath. *A*, Control, immediately after excision; *B*, after 30 min.; *C*, after 1 hr.; *D*, after 4 hr.; *E*, after 8 hr.; *F*, after 18 hr. Tyrode solution oxygenated with oxygen was used in *B*, *C*, *D* and *F*, while Krebs's solution oxygenated with 95 per cent oxygen and 5 per cent carbon dioxide was used in *E*. Temperature of bath, 35° C.

## HISTOCHEMISTRY

### Histochemical Demonstration of Aldehydes by *p*-Phenylenediamine

A highly specific and sensitive reaction has already been proposed[1] for the microscopic detection of aldehydes in the tissues. Improvements have now been made which meet the needs of practical histochemistry.

The oxidation velocity of *p*-phenylenediamine with hydrogen peroxide is greatly increased by aldehydes[2]. Only nitriles, aldehyde ammonia and aldehyde bisulphite compounds behave similarly to aldehydes[3]. The black precipitate formed on the tissues as a consequence of this peroxidase activity of aldehydes in neutral solution was found suitable for microscopic observation after stabilization with gold chloride.

The following reagents are used: (1) 1 per cent *p*-phenylenediamine stock solution (to reduce storage oxidation, previously boiled water must be used and the solution kept in a tightly stoppered dark flask); (2) 1·5 per cent hydrogen peroxide; (3) 1 per cent gold chloride neutral solution.

The procedure used was as follows. Fix and section by any standard technique. Take sections down to distilled water in the usual manner and treat them for release of aldehydic groups (periodic acid was used in the present experiments). Wash thoroughly with distilled water. Before use, mix equal volumes of reagents (1) and (2) and immerse sections for 15 min. (operate in dark dishes, because light accelerates oxidation of *p*-phenylenediamine). Wash thoroughly with several changes of distilled water. Immerse in reagent (3) for 5 min. Wash, dehydrate and mount in the usual way

(Canada balsam). Structures containing aldehyde are stained bluish-violet.

The results obtained with *p*-phenylenediamine using sections treated in this way are comparable with those obtained with Schiff's reagent, though greater sensitivity and selectivity is obtained.

As a control on the selectivity of the method, the following reagents for blocking aldehydic groups were used before treatment with *p*-phenylenediamine: (1) 0·2 per cent 4-nitrophenylhydrazine solution in 50 per cent v/v ethanol containing 1 per cent sodium acetate, incubation for 2 hr. at 60° C.; (2) saturated hydroxylamine hydrochloride, ethanolic solution, 2 hr. at 60° C.; (3) 1 per cent aniline solution in 75 per cent v/v ethanol, 2 hr. at 60° C. All these reagents completely prevented the peroxidase oxidation of *p*-phenylenediamine.

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## PATHOLOGY

### Growth of Tumours in Rats fed with 4-Dimethylaminoazobenzene injected with Homogenized Tumour mixed with Freund Adjuvant

The enhancing (or *XYZ*) effect on the growth of tumour homografts in animals pre-treated with non-living donor tissue first described by Flexner and Jobling[1] led to many fruitful immunogenetic investigations in oncology. In order to explain the phenomenon, several working hypotheses have been evolved: the 'blockage' hypothesis was advocated by Medawar and co-workers[2] and Snell[3], 'immuno-selection' by Hauschka and co-workers[4] and the hypothesis of some 'physiological' alteration in the tumour cells was argued by Kaliss[5]. According to experiments of Casey and co-workers[6], it is possible to enhance the tumour growth in the strain from which the tumour originated. It is difficult to explain these results on the hypotheses mentioned above.

I have tried to enhance the growth of indigenous tumours. Albino rats of mixed breed were subjected to a carcinogenic diet supplied with 4-dimethylaminoazobenzene. The daily dose of 3·5 mgm. of the drug per rat given during a period of 203 days induced liver carcinoma after a latent period of nearly 120 days after stopping the drug. The incidence of hepatoma was 68 per cent.

In the experiment to be described, 120 rats fed 4-dimethylaminoazobenzene for 203 days were divided at random into five groups and injected with normal liver tissue or liver carcinoma of the same origin, both mixed with Freund's adjuvant. The antigen mixture was heated on a water-bath at 60° C. for 45 min. No palpable liver tumour was present in animals at the time of injection, so it was assumed that the animals were in a pre-cancerous stage. The intracutaneous injections, 8 × 0·2 ml. of antigen mixture, were given along both flanks of the rats simultaneously on the fourth day after stopping the carcinogenic diet. The three intraperitoneal injections (1 ml. each of antigen mixture) were given at intervals of 1 week, the first being given on the same day as intracutaneous injections. On the twenty-second day after stopping the carcinogenic diet, the animals were killed, and diagnosis was by gross inspection and histological examinations of the liver.

Table 1. Incidence of Carcinoma Hepatitis in Pre-cancerous Rats treated with Tumour Tissue and Normal Liver Tissue mixed with Adjuvant

| Animals | Treatment | | | | |
|---|---|---|---|---|---|
| | Intraperitoneal | | Intracutaneous | | None |
| | Tumour tissue | Liver tissue | Tumour tissue | Liver tissue | |
| Pre-cancerous | 12/24 | 0/24 | 0/24 | 0/24 | 0/24 |
| Normal | 0/20 | | 0/18 | | |

The results presented in Table 1 show that intraperitoneal application of the antigen mixture containing cancer tissue was in this instance only suitable for inducing growth promotion of the cancer. It is worth mentioning that inflammatory reaction in the abdominal cavity which occurs after intraperitoneal injection of adjuvant alone or mixed with some tissue was negligible in tumour-bearing rats in comparison with other animals injected intraperitoneally.

As already stressed[7], the enhancement of tumour growth and tumour graft may show a specific difference between cancerous and normal tissues. The effect of enhanced tumour growth produced by the stimulating effect of antibodies might be explained simply by assuming that antibodies are complementary bodies, which act on normal tissue by destroying it and on cancerous tissue on the contrary by enhancing its growth. Cachexia and enhanced tumour growth in cancer-bearing animals could thus be ascribed to a manifestation of the same process in tissues of different physiological and functional state. Further experiments are in progress to investigate the problem.

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### Interaction of Enzymes with Normal and Tumour Cells

Wheat germ lipase (Worthington) has been shown[1] to reduce the adhesion of washed mouse ascites cells to glass. This was considered to be due to the adsorption of the enzyme on to the cell surface. The same lipase preparation has also been found[2] to inhibit the growth of hamster kidney tumour cells in tissue culture at certain concentrations (0·01–0·1 per cent), without inhibiting growth *in vitro* of hamster normal kidney epithelial cells from which the tumour was derived.

An investigation has been made into the cytological effects of lipase on these normal and tumour cells growing in tissue culture, using 'Anoptral' contrast microscopy. At an enzyme concentration of 0·1 per cent, the tumour cells showed extensive vacuolation

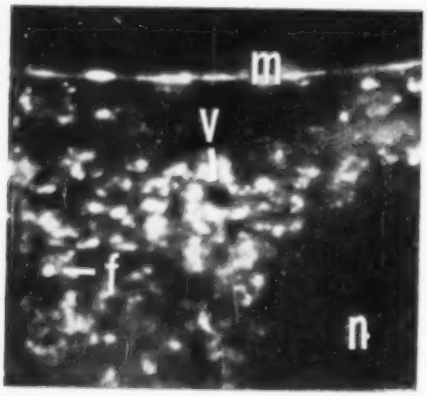


Fig. 1. Marginal part of a normal hamster kidney epithelial cell in a monolayer culture, 5 hr. after adding fluorescein-labelled lipase (0·1 per cent). Ultra-violet illumination (× 1,600). *f*, Fluorescent vacuole; *m*, cell membrane; *n*, nucleus; *v*, non-fluorescent vacuole

of the cytoplasm by the third day after addition. Such vacuolation was not found in treated normal cells.

The site of action of lipase has also been followed, by labelling it directly with the fluorescent dyes fluorescein and lissamine rhodamine *RB* 200 (ref. 3). The enzyme was assayed against triacetin before and after labelling, to check whether the conjugation procedure had destroyed its activity. It was found that the fluorescent conjugate showed half the aliesterase activity of the untreated enzyme. Schiller *et al.*[4] provide evidence that directly labelled protein conjugates are reasonably stable for at least 24 hr. under *in vivo* conditions.

Cultures were incubated in growth medium (0·25 per cent lactalbumin hydrolysate, 10 per cent calf serum, 0·001 per cent sodium bicarbonate) containing 0·1 per cent lipase conjugate. They were mounted in this medium without fixation and observed under a Reichert fluorescence microscope. In the normal cultures, many large and small droplets were taken in within the first few hours, and an intense staining of the cell membrane in some cells was observed 5 hr. after addition. Membrane staining was not observed before this period had elapsed, and was not seen later than 8 hr. after addition. Non-viable cells did not show staining of the cell membrane. As a control, lissamine rhodamine *RB* 200 was applied to growing normal cultures at the same concentration as in the conjugate-treated cultures. The dye was taken in as droplets, but did not stain the membrane.

Tumour cultures also took up many large and small droplets, but there was no obvious staining of the cell membrane, even in cells washed prior to treatment.

Lipase conjugate has also been applied to Landschütz ascites tumour cells at the same concentration, under both *in vivo* and *in vitro* conditions. About 5 per cent of the ascites cells took up pinocytosis droplets *in vivo* during the first day after intraperitoneal injection of the conjugate, but there was no staining of the membrane. Washed ascites cells after 2-hr. treatment with lipase conjugate *in vitro* did, however, show surface staining, confirming that the enzyme is adsorbed on to the surface of washed ascites cells.

Observations using fluorescent-labelled lipase indicate that the conjugate is readily taken up by pinocytosis within a few hours by normal hamster kidney and hamster kidney tumour cells *in vitro*, and by mouse ascites cells *in vivo*. The transient staining of the normal cell membrane, which has not been observed in the tumour cells, suggests that there is some accumulation of the enzyme preparation at the surface. Such an accumulation has not been detected with other fluorescent-labelled enzyme conjugates. The difference in vital staining between the normal and the homologous tumour cells provides further evidence for the altered properties of the tumour cell surface.

We wish to express our gratitude to Dr. R. D. Andrews and his staff of Glaxo Laboratories for preparing the cultures.

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## HÆMATOLOGY

### Acetylcholinesterase and the Life-span of the Erythrocyte

The function of the relatively large amount of the enzyme acetylcholinesterase which is present in erythrocytes is unknown. The enzyme was thought to be essential for the maintenance of normal permeability of the erythrocyte[1], but experiments on cells deficient in acetylcholinesterase[2] have failed to demonstrate this function. Interest in red-cell acetylcholinesterase has been stimulated by the recent finding that in some patients with paroxysmal nocturnal hæmoglobinuria (P.N.H.) the enzyme is deficient[3]. The enzyme activity in patients with P.N.H. varies from 6–134 per cent of average normal activity[4], and there is a correlation between the degree of enzyme deficiency and some other features of P.N.H.[4]. It is thus possible that the shortened erythrocyte life-span in P.N.H. may be related to the enzyme deficiency, and that normal amounts of acetylcholinesterase are necessary for normal survival of erythrocytes.

To determine whether normal levels of acetylcholinesterase are necessary for normal erythrocyte life-span, the enzyme was inhibited *in vivo* in five hæmatologically normal subjects by the administration of octamethylpyrophosphoramide (OMPA) 5 mgm. daily, and erythrocyte survival measured with chromium-51. The administration of OMPA results in irreversible inhibition of erythrocyte acetylcholinesterase[5]. Erythrocyte acetylcholinesterase was measured according to the method of Michel[6]. Erythrocytes were labelled as described by Mollison and Veall[7] and the results expressed as the time taken for circulating radioactivity to reach 50 per cent ($T\frac{1}{2}$ $^{51}$Cr). Mean cell-life was calculated after correcting for elution ($T\frac{1}{2}$ elution 64 days).

In three subjects, erythrocytes were labelled (on day 0) and OMPA administered from day 6 to day 13–18, during which time the enzyme activity was

reduced to less than 50 per cent of the initial level. In spite of deficient acetylcholinesterase during the period of investigation (50 days), erythrocyte life-span was within normal limits in all subjects (Table 1). In two further subjects OMPA was administered for a period of 21 days before labelling the erythrocytes. The life-span of the erythrocytes was within normal limits in both subjects (Table 1).

Table 1

| Case | Duration of administration of OMPA (days) | Erythrocyte acetylcholinesterase (Δ pH/hr.) Before OMPA | After OMPA | $T_{\frac{1}{2}}$ $^{51}Cr$ (days) | Mean cell life (days) |
|---|---|---|---|---|---|
| 1 | 7 | 0·66 | 0·32 | 28 | 110 |
| 2 | 7 | 0·79 | 0·36 | 33 | 111 |
| 3 | 12 | 0·98 | 0·32 | 32 | 113 |
| 4 | 21 | 0·72 | 0·25 | 36 | 120 |
| 5 | 21 | 0·68 | 0·35 | 29 | 114 |

Thus in five subjects where erythrocyte acetylcholinesterase was inhibited to levels comparable to those found in patients with P.N.H., shortening of erythrocyte life-span could not be demonstrated. These results suggest that normal amounts of the enzyme are not essential for the maintenance of red-cell life-span, and that the low levels of enzyme in P.N.H. do not directly contribute to the diminished erythrocyte life-span in the disease.

We wish to thank the Director, South African Institute for Medical Research, for facilities to carry out this work.

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## Fructose as a Component of the Fœtal Blood in Several Mammalian Species

In the examination of fœtal bloods from several mammalian species, Goodwin[1] suggested that fructose is a characteristic component of the fœtal blood of the Ungulata and Cetacea. We wish to support this generalization by reporting the presence of fructose in the fœtal blood and fœtal fluids of several further species within the order Ungulata, and the essential absence in a member of the Edentata.

The specimens from the dromedary were made available through Dr. W. R. M. Morton, of the Queen's University, Belfast, the sloth material obtained while one of us (A. St. G. H.) was in Brazil, through the kindness of Prof. Nelson Chaves, of the University of Recife. The remainder of the specimens were obtained by Mr. Tong and his staff at Whipsnade Zoological Park. Samples were obtained from the placenta at a variable interval of time after extrusion. The material was placed in bottles containing 100 mgm. powdered sodium fluoride and potassium oxalate in the ratio 1 : 3 and refrigerated pending transfer to the laboratory. After deproteinization, the filtrates were estimated for glucose and fructose by the glucose oxidase and resorcinol methods respectively. The concentrations obtained (Table 1) must be considered as minimal values, since there is evidence of a preferential utilization of glucose in the placenta after it is shed.

It is interesting perhaps to note that in the spectrum of mammalian species which have been examined by us and by others[2–4], in which fructose is present in substantial concentrations, all belong to a group of animals having either the epitheliochorial or syndesmochorial type of placenta. The latter type, typified by the sheep, is known from direct experimentation to produce fructose[5].

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## Transferrin-groups of Fœtal Calf-Serum

Intensive work on the occurrence of blood-group factors in embryos of cattle[1] led to the result that the pattern of blood-group factors, as special individual molecule structures, are genetically dependent and, consequently, are already fixed in the mother cells of the erythropoietic system. The substances of the blood groups undergo a maturing process before birth during embryonic and fœtal growth. With the help of strong immunosera, the blood-group factors already can be identified in the early embryonic stage in the immuno-haemolytic and in the inhibition test. The

Table 1. Glucose and Fructose Concentrations in Samples obtained from Species within the Orders Ungulata and Edentata (Mgm./100 ml.)

| Species | Maternal blood Glucose | Maternal blood Fructose | Fœtal blood Glucose | Fœtal blood Fructose | Fœtal fluids* Glucose | Fœtal fluids* Fructose |
|---|---|---|---|---|---|---|
| Père David's deer (*Elaphurus davidianus*) | — | — | 364 | 61 | 12 | 209 |
| Père David's deer (*Elaphurus davidianus*) | — | — | 18 | 57 | 22 | 36 |
| Huanaco (*Lama huanacus*) | — | — | 32 | 148 | 14 | 218 |
| Llama (domestic breed) | — | — | 15 | 43 | 10 | 223 |
| Giraffe (*Giraffa camalopardalis*) | — | — | 8 | 8 | — | — |
| Rhinoceros (*Rhinoceros unicornis*) | — | — | 15 | 31 | — | — |
| Hippopotamus (*Hippopotamus amphibius*) | — | — | 9 | 60 | — | — |
| Bactrian camel (*Camelus bactrianus*) | — | — | — | 84 | — | — |
| Bactrian camel (*Camelus bactrianus*) | — | — | 9 | 63 | 13 | 376 |
| Dromedary camel (*Camelus dromedarius*) | 97 | UA† 0 | 42 | 40 | 6 | 352 |
| Three-toed sloth (*Bradypus tridactylus*) | 124 | UV† 1·5 | 43<br>28 | 41<br>1·5 | 13 | 1·5 |

* Amniotic or allantoic or a mixture of both fluids.
† UA and UV refer to umbilical artery and vein samples respectively.

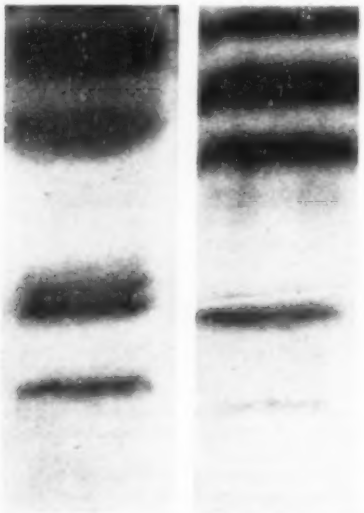

Fig. 1. Left, starch-gel electrophoresis pattern of foetal calf serum (transferrin bands); right, starch-gel electrophoresis of foetal calf serum after 90 per cent enrichment of fetuin (fetuin bands)

youngest cattle embryo, the blood-group factors of which we have already identified, had a head to tail length of 17 mm. This corresponds to an age of 28–35 days.

The study of foetal sera was performed with the help of starch gel electrophoresis[2]. As buffer solution, we used a mixture of *tris*(hydroxymethyl)aminomethane, dicodium salt of ethylenedinitrilotetraacetic acid and boric acid. The migration time of the proteins was 3·5 hr. in an electric field of 7·8 V./cm. Here they showed a clear difference in the albumin/globulin ratio between foetal serum and serum of adult cattle. The serum of embryos and foetuses showed a minor content of beta-globulins and a relatively higher content of alpha-globulins. Between the region of the alpha-globulin complex and the post-albumin region in the serum of adult animals, in foetal sera an additional separation appeared in wide bands (Fig. 1).

By isolating fetuin, which as mucoprotein is a regular part of calf serum, using the precipitation method of Deutsch[3] with a 90 per cent enrichment and a joining starch-gel electrophoresis, we came to the conclusion that the observed additional bands must be attributed to the fetuin fraction.

By the separation of the beta-globulins in the foetal sera, all transferrin-groups until now observed in the serum of adult cattle of highland breeds (Fleckvieh, Brown Swiss) could be shown. Until now, neither with the adult cattle nor with cattle foetuses has the serum-transferrin group *E/E* been discovered.

The smallest embryo from which we could successfully get enough serum for starch-gel electrophoresis had a head-to-tail length of 42 mm., corresponding to an age of 7 weeks.

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## RADIOBIOLOGY

### Changes in X-ray Sensitivity of HeLa Cells during the Division Cycle

Measurement by Puck and Marcus of the reproductive survival of randomly dividing cultures of HeLa *S3* cells after X-irradiation revealed an exponential response to dose following a shoulder[1]. However, the possibility was not excluded that these populations are in fact heterogeneous, the cells undergoing small, or large but brief, fluctuations in sensitivity during the division cycle. We have examined this possibility by irradiating synchronously growing populations at various times after mitosis.

Synchrony was achieved by selectively harvesting mitotic cells from cultures of HeLa *S3–9IV* (ref. 2) growing as monolayers in medium *N16HHF* (ref. 3). Dividing cells, being less firmly attached to the plastic culture vessels, were removed by repeated rinsing with growth medium. About 1 per cent of the cells were so gathered, and 80–90 per cent of them were in metaphase to late telophase. Their plating efficiency was 84–90 per cent; 90–100 per cent of those which attached to new plastic culture dishes completed division within 3 hr. after collection. The next division cycle did not commence for an additional 17–21 hr. Fig. 1 shows typical growth-curves for synchronous and random cultures, as determined by repeated microscopic observations of specified fields[4]. The rise in mitotic frequency in the synchronous culture at about the time of division is also shown in Fig. 1. Details of this technique will be reported more fully elsewhere.

Fig. 2 shows typical survival curves obtained for cells irradiated at 37° with 220 kev. X-rays (constant potential; 15 m.amp.; 1 mm. aluminium + 0·5 mm. copper added filtration; about 30 rads per min.; half-value layer 1·9 mm. copper) at selected times after collection. The zero-hour curve represents cells in mitosis, and if the time-course of the synthesis of deoxy-

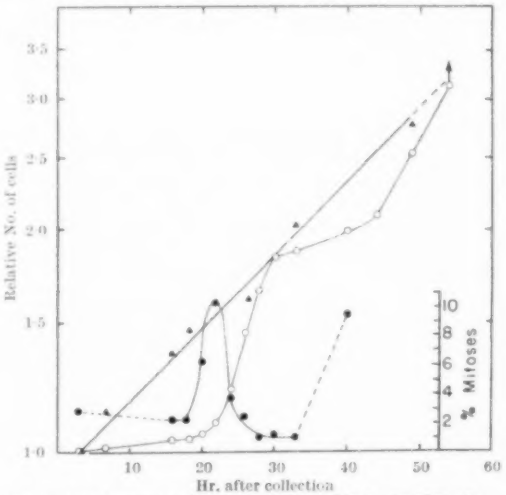


Fig. 1. Synchronous and random division of HeLa *S3-9IV* cells. Relative cell numbers, as determined by repeated microscopic observation of specified fields, and mitotic activity, as determined from stained preparations, are plotted as functions of time after harvesting mitotic cells. The cell counts at 3 hr. were 103 for the synchronous culture, and 94 for the random culture. The arrow at 54 hr. indicates that the value plotted was a minimum one. ▲, Random population; ○, synchronized population; ●, mitotic frequency

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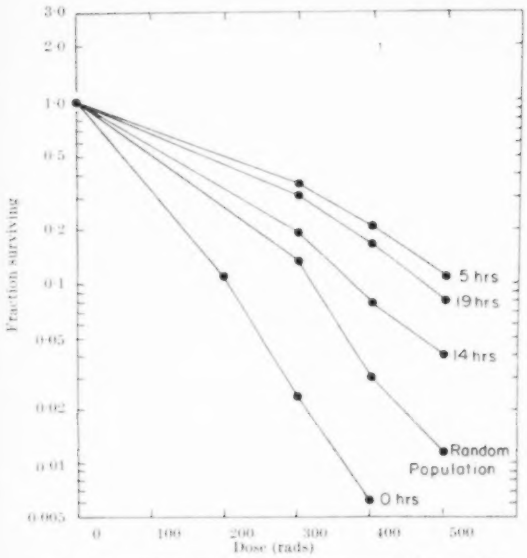


Fig. 2. Survival of colony-forming capacity of HeLa *S3-9IV* cells after irradiation with 220 keV. X-rays at the times in the division cycle indicated. Random population was irradiated immediately after trypsinization, while cells were still in suspension; 3 hr. later such cells showed a lower sensitivity

ribonucleic acid (DNA) as determined by Painter and Drew[5] for HeLa *S3* cells applies to our system, then 5 hr. after cell collection lies in the pre-synthetic ($G_1$) phase, 14 hr. in the synthetic (*S*) phase, and 19 hr. in the pre-mitotic ($G_2$) phase.

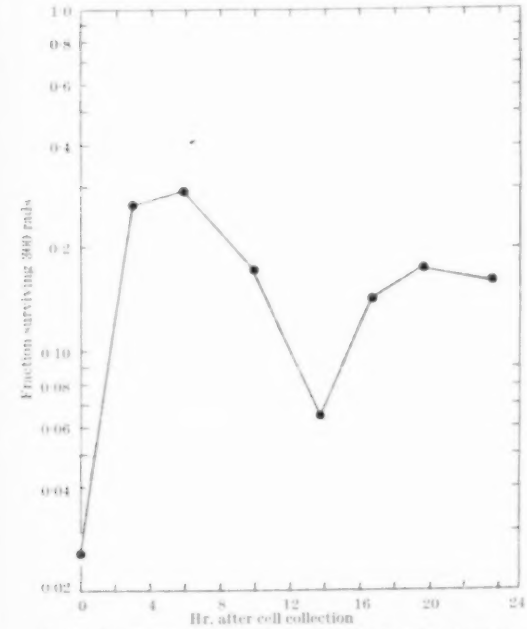


Fig. 3. Fractional survival of HeLa *S3-9I V* cells after exposure to 220 keV. X-rays at various times during the division cycle. Data obtained from single doses of 300 rads are plotted on semi-logarithmic co-ordinates, as this representation corresponds to changes in mean lethal dose, if the extrapolation number is constant

It is clear that mitotic cells are more sensitive (mean lethal dose, $D_0 = 59$–82 rads) than are random populations ($D_0 = 100$–120 rads). Such heightened sensitivity is probably correlated with the condensed state of mitotic chromosomes[6]; increased chromosome damage has previously been observed in cells during mitosis[7]. We are unable, with this technique, to determine changes during the various phases of mitosis.

Fluctuations in sensitivity also occur during interphase. As shown in the data of Figs. 2 and 3 (the latter showing cell survival following administration of 300 rads at different times in the division cycle), and of several other experiments, cells are relatively resistant 3–7 hr. after collecting, become progressively more sensitive during the period 7–14 hr., and then more resistant again from 14–18 hr. The data do not permit detection of small changes in extrapolation number during the cycle, but no gross changes are apparent. Accordingly, most or all the fluctuation shown in Figs. 2 and 3 is attributable to changes in $D_0$. Making this assumption, in four experiments $D_0$ decreased 16–60 per cent between 3–7 and 14 hr.

The causes of these intermitotic fluctuations in sensitivity are not apparent. The occurrence of a peak in sensitivity at about 14 hr. after mitosis suggests that no simple model will account for the fluctuations, which may result from alterations in damage, or in repair processes, or both. Further indications of the complexity of the system have been found in other experiments (Terasima, T., and Tolmach, L. J., unpublished work) which show that X-ray-induced divisional lag fluctuates in parallel with sensitivity from zero to 14 hr. after mitosis, but not over the remainder of the cycle.

This investigation was supported in part by a grant (*C*–4483) from the U.S. Public Health Service.

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## Trace-labelling of Insulin with Iodine

A recent technique for the immunological assay of human plasma insulin requires a radioactive bovine insulin of very high specific activity[1].

Crystalline bovine insulin is labelled with iodine-131 using the only method reported to produce a suitable activity, to the order of 75–300 mc. iodine-131/mgm. insulin[2]. We encountered some difficulties with this method and have made certain modifications. The following procedure has proved more reliable, consistently yielding a specific activity of 300–600 mc. iodine-131/mgm. insulin. Also there is less radiation hazard in that chloroform extraction of up to 80 mc. of iodine-131, part of the original method, is avoided,

and so the number of transfers of solutions of high radioactivity into different containers is reduced.

20 μl. of iodine monochloride and 10–20 mc. of thiosulphate-free, carrier-free iodine-131 in minimal $N/50$ sodium hydroxide are added virtually simultaneously to a fresh solution of 20 μgm. of crystalline bovine insulin in borate buffer, *p*H 7·8, in a perfectly clean glass tube[3]. The tube, sealed by a secure glass stopper, is shaken vigorously for 4 min., and a third of the insulin is immediately dialysed. Several changes of distilled water, 2 l. at a time, rid the protein solution of unbound iodine-131.

Some insulin is inevitably damaged by irradiation. The amount damaged is roughly proportional to the specific activity. The damaged fraction is separated from the undamaged fraction on a cellulose column[2]. Damaged insulin labelled with iodine-131 is biologically and immunologically inactive and runs just behind albumin on chromato-electrophoresis on Whatman 3 *MM* paper strips, while the undamaged 'free' insulin is adsorbed at the origin (Fig. 1). After purification almost all the damaged fraction is removed (Fig. 2). The undamaged insulin is now available for investigation requiring truly tracer quantities of radioactive hormone.

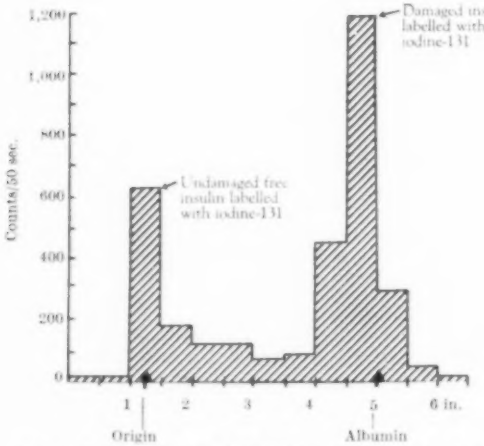


Fig. 1. Damaged insulin labelled with iodine-131 predominates on scanning the radioactivity of a paper strip after chromato-electrophoresis of the first fraction collected from a cellulose column, during purification of crystalline bovine insulin labelled with iodine-131 (specific activity 550 mc. iodine-131/mgm. insulin). Human plasma was present in this mixture

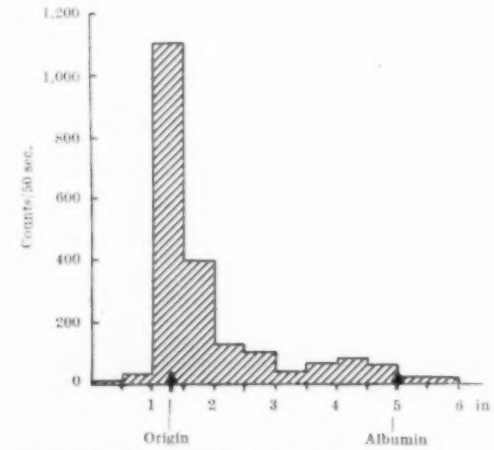


Fig. 2. Radio-chromato-electrophoretograms of a later eluate from the cellulose column, showing purified, 'free' insulin labelled with iodine-131 adsorbed at the origin

It has been suggested that damaged insulin binds indiscriminately to serum proteins and hence migrates away from the origin. We have found, however, that a solution containing damaged insulin, free of serum and albumin, shows identical migration of damaged insulin, as in Fig. 1. We have also separated the two fractions on cellulose acetate strips pre-soaked in non-radioactive insulin, confirming that damaged insulin has an electrophoretic mobility of its own.

This work was supported by the Medical Research Council and the British Insulin Manufacturers.

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## Radiation Effect on Yeasts of the Genus *Candida* Berkhout

So far investigations of radiation damage on yeasts were solely done on ascosporogenous yeasts of the genus *Saccharomyces* (Meyen) Reess, mostly on the species *cerevisiae* Hansen. Major radiation damage to this genus is known[1–4]. We irradiated an anascosporogenous yeast *Candida tropicalis* (Cast.) Berkh. with X-rays (1·54 Å.) and ultra-violet light. This genus is characterized by the ability to form pseudomycelium, that is, filaments similar to the hyphæ of moulds, but consisting of elongated cells which have originated by budding. Formation of pseudomycelium takes place when growth goes on and cell division (budding) is inhibited. By irradiation of *C. tropicalis* we found all the types of radiation damage discussed in refs. 1–4 and a new radiation effect, the formation of pseudomycelium. The equations of the regression-lines for this effect are: X-rays, $y = 3{\cdot}18 + 2{\cdot}78x$; $PPD_{50} = 3{\cdot}6$–$4{\cdot}47$–$5{\cdot}13$ kr. Ultra-violet light: $y = -3{\cdot}66 + 4{\cdot}7x$; $PPD_{50} = 64{\cdot}5$–$69{\cdot}7$–$74{\cdot}1$ sec.

$PPD_{50}$ is the dose necessary to induce in 50 per cent of the irradiated cells the formation of pseudomycelium. It seems interesting to note that simultaneously with the formation of pseudomycelium, the cells lose their Gram-positivity to become Gram-negative instead. Gram-positivity is a function of ribonucleoproteins; by destroying or extracting them, the cells become Gram-negative. So, as a result of irradiation by ultra-violet light or X-rays (1·54 Å.), the metabolism of ribonucleic acid (RNA) is disturbed. In the case of X-rays, the formation of pseudomycelium results much earlier than the induction of lethal mutations, $PPD_{50} = 4{\cdot}47$ kr., whereas $LD_{50} = 10$ kr. So the first attack of X-rays on yeasts of the genus *Candida* is inhibition of cell division, expressing itself in formation of pseudomycelium coupled with damaging of the metabolism of RNA.

Coloration of the irradiated cells with Unna-Pappenheim-stain (after Brachet) confirms the extensive damaging of the metabolism of RNA.

A possible explanation that the first attack is to be found in the inhibition of budding, combined with the damaging of the synthesis of RNA, could be found in the fact that in both cases sulphydryl enzymes are involved.

W. J. Nickerson and G. Falcone[5] described evidence supporting the conclusion that the process of cellular division in yeasts is the result of a chain of events, beginning with transfer of hydrogen by protein-disulphide-reductase to —S—S— linkages in a polysaccharide-protein complex of the yeast cell-wall. Thus rupture of covalent bonds in this major component of the cell wall becomes possible. Following this hypothesis[5], the free radicals produced by irradiation would oxidize the SH-groups and so make budding impossible since pseudomycelium is formed. That this is the case is supported by the fact that by feeding certain sulphydryl-compounds to *Candida* for irradiation (*M*/300 thiourea in glucose-peptone-solution for 18 hr. under continuous stirring at 27°) all the radiation damage is greatly reduced.

This work forms part of a research work contract from the International Atomic Energy Commission, Vienna.

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## BIOLOGY

### A Rare Earless Monitor Lizard from Borneo

*Lanthonotus borneensis* Steindachner—the Borneo earless monitor lizard (which forms, with two American lizards, the family Helodermatidae) is known from less than ten specimens, all from Sarawak (three in Kuching, one in Singapore, the rest in American and British museums), none of which has been collected in recent times or with satisfactory field data. Thus, although the importance of this reptile's purely taxonomic characters in lizard-snake evolution has been examined in detail[1], no supporting information on behaviour has been available.

For some years this Museum has been associated with the Chicago Natural History Museum in a reptile-amphibian collecting project[2], under the general guidance of its curator, Dr. R. Inger. Particular attention has been devoted to a search for *Lanthonotus* throughout West Borneo. Not until January 1961 was any positive report obtained. Then, a live specimen measuring 13 in. (about average size to date) was obtained only a mile from our own archæological base camp at the Great Caves of Niah, centre of intensive reptile collecting since 1954.

After an initial period in which the lizard refused any sort of food and spent most of the time in a state resembling a coma (superficially 'dead') it then responded to the raw eggs of the green turtle, *Chelonia mydas*, the distribution of which in Sarawak happens to be controlled by this Museum[3]. It sucked raw turtle yolk every night for two months. Then circumstances made us bring it back to Niah, where fresh turtle eggs are not available. Chicken eggs were accepted as substitutes; but the animal died on April 11, 1961.

In most of its behaviour it resembled a nocturnal snake. Though taken from a hole in the ground, the front legs are so weak that it is difficult to conceive of its burrowing with these. The strong snout and head were used to enlarge any ground weakness, however. A very good swimmer, it could relax on the bottom of a tank for up to half an hour. This capacity to relax was also a striking characteristic on land; when resting it could literally collapse along the whole length of the body. Then, with very low, slow respiration it was difficult to decide whether it was alive. Evidently, in a natural state, it is able to remain dormant for long periods underground without food and very little air. This, plus nocturnalism and a capacity to carry about earth adhering to the nodular skin, make it most difficult to notice.

When handled, however, it would quickly flatten the body into semi-rigidity. It soon showed evidence of enjoying handling and became 'tame', in a way already known for the related 'Gila monster' *Heloderma suspectum*[4]. It showed no inclination to bite either the handler or anything else (including food). It seems unlikely, therefore, that it is poisonous as has often been suggested[5].

Detailed day and night observations and film records have been made[6]. Further search is continuing at Niah; the results so far are negative.

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### Growth Substances separated from the Root of Water Hyacinth by Paper Chromatography

Evidence for the presence of growth substances in the root extract of water hyacinth (*Eichhornia speciosa* Kunth), presumably related to the rapid multiplication of the weed, has been reported previously from this laboratory[1]. A comparison of the effects of the extract with those of indole acetic acid or gibberellic acid indicated a different substance or substances present in the extract.

Paper chromatographic separation has now been attempted to reveal the nature of the active factors. 30 gm. of fresh root were extracted with chilled absolute alcohol at 0° C. for 18 hr. The extract was filtered and alcohol distilled off under reduced pressure. The aqueous residue was acidified with sulphuric acid to *p*H 3 and extracted with peroxide-free ether for 1½ hr. The ether-soluble factors were then partitioned into acidic and neutral fractions following Kefford[2]. The ether-insoluble substances were neutralized with barium hydroxide, filtered and evaporated to dryness. The dry mass was then dissolved in 0·5 ml. of distilled water and treated overnight with 0·5 ml. of absolute alcohol for chromatography. Acid and neutral ether fractions were evaporated separately and the dry mass dissolved in

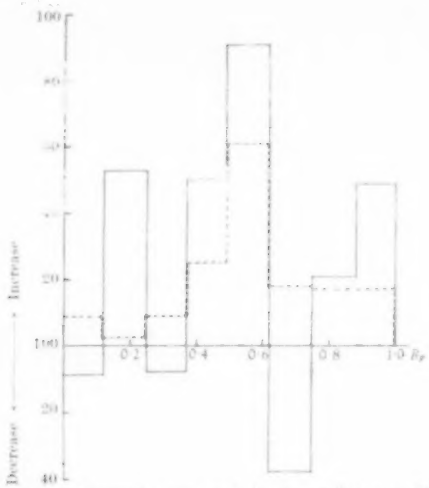


Fig. 1. Root growth (——) and shoot growth (- - - -) of rice seedlings treated with the ether-insoluble water fraction. Solvent: *iso*propanol : ammonia : water

1 ml. of dry peroxide-free ether or absolute alcohol. Three fractions were then chromatographed in Whatman paper No. 1 for 6–8 hr. with *iso*propanol/ammonia/water (16 : 3 : 1). After running the solvent for 20 cm., the air-dried filter paper was cut into 8 pieces and eluted overnight with distilled water in the cold. Root and shoot growth of the intact sprouted rice seed var. Chinsurah Boro in the eluates was used for the bioassay of growth substances. Chemical identification was sought from the $R_F$ of chromatograms with different solvents: *iso*propanol/ammonia/water (16 : 3 : 1); benzene/acetic acid/water (4 : 1 : 2); alcohol/water (7 : 3) and *n*-butanol/acetic acid/water (4 : 1 : 1).

In the neutral ether fraction, no growth-promoting substance was detected either by bioassay or spot colour reaction. The acid-ether fraction did not show significant growth promotion in bioassay, but the colour reactions of the chromatograms run with *iso*propanol/ammonia/water were noticed at $R_F$ 0·73–0·75, 0·76 and 0·91–0·99. The growth substance at $R_F$ 0·73–0·75 was indole-3-acetic acid as confirmed by synthetic indole-3-acetic acid run with the extract in different solvents. The colour reaction at $R_F$ 0·76 was obtained by potassium permanganate, but not with Salkowski or Ehrlich reagent, and was also inactive in the rice-seedling bioassay. The growth factor at $R_F$ 0·91–0·99 appeared to be an indole compound as it gave a spot colour reaction with Salkowski and Ehrlich reagents. The ether-insoluble or aqueous fraction showed marked promotion of growth at three zones: $R_F$ 0·12–0·25, 0·37–0·62 and 0·75–1·0 (Fig. 1). Inhibition of root growth was also observed at $R_F$ 0·62–0·75. Positive Salkowski and Ehrlich reactions were given by the fractions with $R_F$ 0·71–0·75 and 0·97–0·99, suggesting the presence of indole compounds. It is interesting to note that the substance present in the fraction with $R_F$ 0·49–0·60 has marked growth-promoting activities both in the root and shoot of the test material. It gives a colour reaction with potassium permanganate like gibberellic acid but at widely different $R_F$. On the basis of these results it is concluded that the root extract of water hyacinth contains growth substances in addition to indole compounds or gibberellins.

Further work on the chemical nature and properties of the substances is in progress in this laboratory.

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[illegible]

## Life-span of the Fronds of the Giant Kelp, *Macrocystis pyrifera*

The large brown attached alga, *Macrocystis pyrifera*, member of a widespread genus, is of considerable importance as the direct and indirect source of food for a large number of near-shore animals; it is also gathered by man, to be used as fertilizer, food additives, and it is processed for certain of its chemical constituents. The fronds develop continuously from growing points located on the perennial hold-fast at the base of the plant[1]. Little information exists about the life-span of the fronds, although this is a factor of considerable importance in management of the resource and in computing the productivity of the kelp groves. Authors have estimated the life-span as several months[1,2]. Further information is now available as a by-product of work on rate of growth in several kelp-beds spread over a geographical range of about 150 km.

Individual fronds were tagged with numbered small white plastic squares, by divers using self-contained underwater breathing apparatus (SCUBA)[3]. Two tags were attached to each frond by a rubber band loosely encircling the stipe; thus if one marker disappeared, replacement could be effected without loss of the identity of the frond (in practice, however, few tags were lost). Two or more fronds per plant were always tagged. It has always been possible to relocate the plant on subsequent visits, except when the entire organism was removed by a storm or by concentrated grazing. Elimination of the parent plant was disregarded in the statistical calculations of the loss of fronds.

Results for eleven different time periods and three locations are presented in Table 1. For work on rate of growth, fronds were tagged when quite small, 30–100 cm. long; measurements of length were made at intervals as they developed. Experiments 1, 2, 4 and 5 show consecutive measurements on groups of fronds tagged at the beginning of each series. For experiments 2 and 3 many of these time-intervals are lumped in Table 1 and only a few of the visits are represented. In preparing Table 1, a frond was considered as being defunct when it had lost the distal growing tip from which all its blades originate. Measurements have shown that although elongation can occur after loss of this apical blade, overall growth-rates quickly slow down and no more blades are produced (as was also observed in *Macrocystis integrifolia*[1]).

The first experiment in Table 1 summarizes a long-term investigation that began with a large number of young stipes. Experiment 4 in Table 1 was started at about the same time, at Pt. Loma, about 16 km. away. Both beds showed similar rates of mortality, but the Pt. Loma site was abandoned after the final observations shown in experiment 4*b*

Table 1. Mortality of *Macrocystis pyrifera* Fronds at Different Seasons and Locations

| Experiment | Dates of observations: Initial | Dates of observations: Subsequent | No. of intact tagged fronds: Initial | No. of intact tagged fronds: Subsequent | Elapsed time (days) | Loss (per cent) | Half-life (days) | Depth (m.) |
|---|---|---|---|---|---|---|---|---|
| (1) (La Jolla)* | | | | | | | | |
| *a* | 6/12/59 | 7/1/60 | 66 | 25 | 32 | 62 | 23 | 20 |
| *b* | 7/1/60 | 16/5/60 | 25 | 0† | 141 | 100 | — | 20 |
| (2) (La Jolla) | | | | | | | | |
| *a* | 9/5/60 | 20/7/60 | 9 | 8 | 72 | 11 | 400 | 20 |
| *b* | 20/7/60 | 22/9/60 | 8 | 3‡ | 33 | 63 | 24 | 20 |
| (3) (La Jolla) | 23/7/60 | 22/8/60 | 14 | 13 | 45 | 7 | 340 | 20 |
| (4) (Pt. Loma) | | | | | | | | |
| *a* | 28/12/60 | 22/1/60 | 106 | 74 | 25 | 30 | 47 | 15 |
| *b* | 22/1/60 | 18/2/60 | 34 | 23 | 27 | 32 | 48 | 15 |
| (5) (Punta Banda) | | | | | | | | |
| *a* | 28/6/60 | 26/7/60 | 49 | 24 | 28 | 51 | 27 | 2–16 |
| *b* | 26/7/60 | 21/8/60 | 24 | 18 | 16 | 25 | 38 | 2–16 |
| *c* | 11/8/60 | 2/9/60 | 14 | 7 | 22 | 50 | 27 | 2–16 |
| *d* | 2/9/60 | 23/9/60 | 7 | 2 | 21 | 71 | 15 | 2–16 |

* A composite sample of plants along a straight transect line 125 m. long; experiments 2 and 3 were conducted on 2 groups of plants along this same line, separated by about 100 m.

† 3 incomplete fronds were found remaining.

‡ These 3 fronds, although complete, seemed unhealthy, fragile and brittle, and were heavily grazed and encrusted.

because of the encroachment of a horde of sea-urchins, *Strongylocentrotus franciscanus*, which destroyed all the plants at their bases. At La Jolla, in experiment 1, only 3 incomplete fronds remained after 162 days, and these bore evidences of heavy grazing and deterioration. Their lengths were 28, 32 and 35 m.; the stipes were so fragile and chewed that they broke in several places during recovery and measurement, although extreme care was used in handling. Had the fronds been complete, their lengths would probably have been increased by perhaps as much as 5–10 m. Growing conditions during the period of this experiment were favourable with respect to temperature and water clarity, throughout the water column, but a series of storms presumably took a considerable toll of both the Pt. Loma and the La Jolla fronds.

Experiments 2 and 3 describe late spring and summer observations on other groups of fronds when the ocean was comparatively calm. After 72 days, only 1 of the original 9 fronds in experiment 2 had broken, indicating a much slower rate of mortality than had been observed in the winter and spring in experiments 1 and 4. Subsequent to the final observation of this group, the fronds grew up into the warm water above the thermocline and rates of growth quickly decreased practically to nil. All the fronds took on an unhealthy appearance, involving loss of pigment, and became brittle. The mortality-rate increased markedly. A younger set of 14 fronds nearby, below the thermocline, constituting experiment 3, exhibited a very low rate of mortality and normal growth-rates during the period when the older fronds of experiment 2 were suffering heavy losses.

Experiments 5*a–d*, which were run consecutively in a very small bed in a cold upwelling area at Punta Banda, Baja California, illustrate a continuous attrition process, as was likewise demonstrated by experiments 1 and 4. The loss per unit of time was somewhat variable in this bed. The half-life expectation of the fronds ranged from 12 to 38 days (Table 1). These values compare with a winter half-life of 23 days at La Jolla (experiment 1) and of 47 to 48 days at Pt. Loma (experiment 4). The chief damaging factor in the Punta Banda bed was apparently an excessively thick and continuing encrustation of the bryozoan *Membranipora serrilamella*, which restricted growth, deformed the tissues, and induced brittleness and breakage by water movements.

It is apparent from the examples just cited that considerations of the life-span of kelp fronds can be quite complex. It is important to define accurately the terms used. In some circumstances the average age of a group may be considerably less than the maximum age. The age of our experimental fronds at the time of tagging may be safely estimated from our growth data as ± 2 months, hence the observations indicate that the maximum age of a frond in 20 m. of water under favourable growing conditions is about 6 months, confirming the values of Scagel[1] and Brandt[2]. The average age, however, may often be only 2–3 months.

If unfavourable conditions, such as the temperature destruction of the fronds in experiment 2, develop suddenly, the maximum age of a population of fronds may almost coincide with the average age, and may be substantially less than 6 months.

Support of this work by the California Department of Fish and Game and the State Water Pollution Control Board is gratefully acknowledged.

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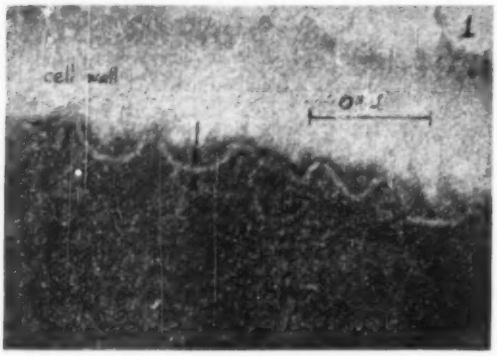
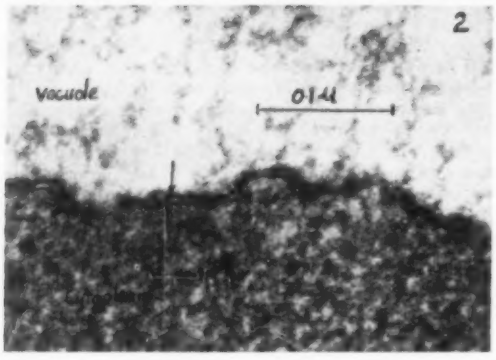
## Method for revealing the Membrane Systems in Micro-organisms

The use of potassium permanganate as a biological fixative for revealing the membrane systems of cells is well known to electron microscopists[1]. This fixative has been successful in preserving the fine morphology of bacteria and yeast; but, up to date, workers have failed to show the true nature of the membranes in these organisms[2,3]. This communication describes a method for stabilizing and increasing the electron density of membranes in micro-organisms by post-fixing them with a uranium salt.

The organisms are fixed in suspension with a 2 per cent solution of potassium permanganate buffered with veronal acetate. This is followed by washing them in several changes with a 2 per cent solution of uranyl nitrate and allowing them to remain in the



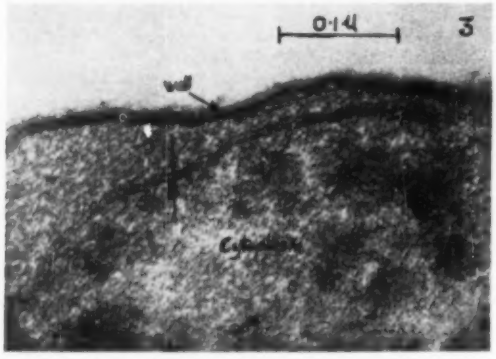




Fig. 1. Yeast cell wall and the cytoplasmic unit membrane

Fig. 2. Yeast vacuolar membrane

Fig. 3. Wall of *Rhizobium* and the limiting cytoplasmic membrane

final change for 1 hr. Washing, dehydration, embedding and sectioning are then carried out in the conventional manner.

Robertson[4,5] regards the unit membrane as two protein layers each about 20 Å. thick separated by a lipid layer approximately 35 Å. thick. The use of post-fixation has enabled me to resolve these layers in the nuclear membrane, cytoplasmic membrane, mitochondrial membranes and vacuolar membrane of yeast and has also enabled me to show a limiting cytoplasmic unit membrane in the bacterium *Rhizobium trifolii*.

In the three electron micrographs (Figs. 1–3) the components of the unit membranes are resolved. The two electron-dense lines represent the protein layers and the clear space dividing them the lipid layer.

I prefer to call the uranyl nitrate treatment a post-fixation since, fixing with permanganate followed by the staining of sections with uranium on the grid in the usual fashion fails to show the membranes satisfactorily. It appears that post-fixation retains something in addition to that retained by the permanganate alone.

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## Function of the Caudal Appendage of *Priapulus caudatus*

The caudal appendage of *Priapulus* consists of a central hollow stalk from which numerous finger-like tubes project. The lumen of the appendage communicates with the voluminous coelomic cavity by an opening surrounded by circular muscles[1]. Several authors ascribe a respiratory function to the appendage[2,3], but other theories have also been proposed[4]. The following observations may throw light on the function of the appendage.

Ten specimens of *Priapulus caudatus* were stored overnight in 100 ml. sea-water. The next day the animals were motionless and probably asphyxiated, but when new sea-water was added the animals started lively movements. At intervals the caudal appendage and its processes contracted vigorously (Fig. 1), injecting coelomic fluid into the body cavity. Shortly afterwards the appendage relaxed and coelomic fluid streamed back into it. The streaming of coelomic corpuscles could be observed through the transparent walls of the appendage. In other experiments specimens of *Priapulus* were asphyxiated by bubbling nitrogen through the water. Also in these cases rhythmical contractions and relaxations of the caudal appendage followed the addition of aerated sea-water.

From the observations, it seems probable that the caudal appendage has a respiratory function. Its

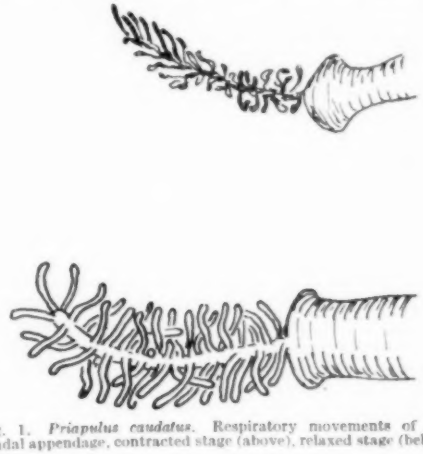

Fig. 1. *Priapulus caudatus*. Respiratory movements of the caudal appendage, contracted stage (above), relaxed stage (below)

thin walls allow a rapid uptake of oxygen, and the rhythmic muscular contractions bring oxygenated cœlomic fluid into the body cavity. The presence of a respiratory pigment in the cœlomocytes[5,6] makes the cœlomic fluid well suited for transport of oxygen. That the pigment is a haemerythrin, as stated previously[5,6], was confirmed by a spectrophotometric examination of a haemolysate with distilled water. The appearance of an absorption maximum at 4900 Å. agrees well with observations on *Sipunculus*[7,8].

In spite of its content of a respiratory pigment the oxygen capacity of the cœlomic fluid is rather small. By measurements with a van Slyke apparatus the value of 0·014 ml. oxygen per ml. fluid was obtained. For sea-water the value 0·006–0·007 was found. The oxygen dissociation properties of cœlomic fluid was studied by a crude colorimetric method. Half saturation was obtained at an oxygen tension of 60 mm. mercury, which indicates a slowly sloping dissociation curve. However, the measurements were made at 19° C., which is above the temperature of the natural environment of *Priapulus caudatus*.

It is an unsolved problem how respiratory movements of the caudal appendage can be triggered by an increase of oxygen tension in the surrounding sea-water. Probably, the movements are initiated from the nervous system, because the muscles of the appendage are innervated from the abdominal nerve trunk[1].

We are grateful to Dr. Knut Schmidt-Nielsen of Duke University, Durham, North Carolina, who made the van Slyke analyses.

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## ANATOMY

### Properties of Stressed Bone

PROF. DREYER'S communication[1] raises a matter of considerable interest and importance. Engineers know that all materials react similarly on broad principles. That is, they obey Hooke's law, within wide ranges, of course, and conform to other physical changes under stress such as Poisson's ratio.

There is no reason to doubt that bone material differs in principle from other created material. As such it should be, and probably is, elastic up to a yield point. Experiments on living bone may be difficult, but if Young's modulus for bone tissue, or the range of elastic limit, could be determined it would be most helpful. Moreover, its subsequent behaviour beyond that point up to fracture should be established, and would then provide an answer to the problem under investigation by Prof. Dreyer.

Moreover, the amount of compression and extension under stress, as well as the degree of bending under torque, or eccentric loading, are clearly forms of bone characteristics that ought to be known. Naturally the reactions on colour referred to by Prof. Dreyer are a measure of the reaction set up to applied stresses, and are familiar to every engineer. 'Perspex' and celluloid, in the form of full-size models, indicate changes in colour under stress, and show the pattern and distribution of stresses set up under applied loads. They can also be used to reveal the effects and redistribution of stress under fatigue due to repetitive loading. A breakdown then occurs of normal strength leading to failure at a much lower stress. This, of course, is of considerable importance with a lowering of the elastic limit by age.

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THE problem that needs elucidation is to determine the nature and origin of the osteoblastic and osteoclastic stimuli which, when associated with a normal metabolism, will influence the deposition or removal of bone.

These stimuli may originate as a result of function or non-function of a bone. It is therefore tempting to suggest that stress produces some change in the inorganic or organic portion of the bone. The stress is then converted to a stimulus which affects the neighbouring osteogenic tissue.

The crystalline structure of bone had led us to believe that these stimuli may be electrical. The piezoelectric properties of bone have been investigated, but so far my results have not been encouraging. Thus when I found the alteration in staining properties and birefringence of bone as a result of stress I felt that these changes may well be related to the origin of locally produced osteoblastic and osteoclastic stimuli in bone.

I am not sure that the phenomenon that I have described is quite comparable with the changes seen in colour in stressed 'Perspex', celluloid, transparent 'Balelite' and 'Araldite' (Ciba).

When these materials are stressed with mild forces the changes in colour occur almost immediately and conversely disappear as soon as the force is released. My *in vitro* experiments show that the birefringent portion of the bone does not, even after 24 hr., revert to its unstressed state when the stress is removed; yet *in vivo* this must be a reversible process. Of course, the picture with massive forces and the influence of temperature is an entirely different matter.

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### Influence of Large Doses of Œstrogens on the Structure of the Bones of Some Reptiles

IT was first shown by Kyes and Potter[1] that, during reproductive activity, the marrow cavities of the bones of female pigeons become filled with endosteal bone. It is thought that this medullary bone is formed under the synergistic action of the androgens and œstrogens[2] which are produced in the female bird during the breeding season. Similarly, injections of œstrogens induce the formation of medullary bone in

male birds. Medullary bone differs from cortical bone histologically[2,3], and it appears to act as a labile calcium store which can be mobilized rapidly during the formation of the eggshell.

Although medullary bone has been found in all species of birds which have been investigated it has only been possible to demonstrate it in one species of mammal, the mouse[3], although six other species have been investigated. Medullary bone never occurs naturally in mice and there is in fact evidence to suggest that even when it is induced experimentally it differs from that which occurs normally in birds[6].

The question arises therefore whether the early reptiles possessed medullary bone, and the ability to form it has been lost in mammals with the loss of the calcified eggshell; or whether the ability to store calcium in this way has been evolved only in the birds.

Some answer to this question is provided in the recent work of Edgren[7], who found that there was a fall in the density of the bones of female turtles during the reproductive season. This indicates that calcium is withdrawn from the long bones of the limbs to provide calcium for the eggshell. If calcium were stored before the formation of the eggshell, this would have been detected as an increase in the density of the bones, but this was not found. This would appear to indicate that there is no formation of medullary bone which could act as a special store of calcium, but that the cortical bone is resorbed during the formation of the eggshell.

The work reported here concerns two observations which are pertinent to the scheme implied by Edgren's work. A male eastern painted turtle, *Chrysemys picta picta*, was caught, in Georgia, United States, during August and given an initial injection of 1 mgm. of œstrone (10,000 International Units) in 1 ml. of peanut oil. The animal was then given daily intramuscular injections, into alternate hind limbs, of 5,000 I.U. of this hormone for 12 days and it was then killed. At death it weighed 200 gm., of which the shell comprised 63·5 gm. The femurs were cleaned and fixed in 5 per cent formalin. Pieces of bone were decalcified and sectioned.

A similar experiment was performed on a female gopher tortoise, *Gopher polyphemus*, which at death weighed 350 gm., of which the shell comprised 169·5 gm. Although the ovary contained ova of up to 1 cm. in diameter, there were no eggs in the oviduct. The femurs were again examined histologically.

The bones from these animals contained many trabeculæ, possibly related to their curved shape. There was no medullary bone present. Methylene blue extinction values were taken at various *p*H-levels using barbitone buffers[8]. In both cases the bone had values of about *p*H 4, whereas avian medullary bone has a value below *p*H 3 (ref. 4).

The experiments described must be regarded as preliminary ones, but they provide evidence from an entirely independent source to confirm the system suggested by the work of Edgren. Thus it appears that these Chelonia do not form medullary bone under the influence of the sex hormones and do not store calcium before egg-laying. There is therefore a definite difference in the calcium metabolism of these reptiles and the birds.

It is a pleasure to acknowledge the assistance of Hugo Greiner and Miss E. M. H. Wilson in these experiments. The work reported was performed in the Anatomy Department, Emory University, Georgia, United States, through the hospitality of Prof. G. H. Bourne and during the tenure of a Lalor Foundation research award for the summer of 1960 and a Wellcome research travel grant.

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## IMMUNOLOGY

### Partial Inhibition of Antibody Formation by means of Anti-Ribonucleoprotein Serum

Nucleoproteins seem to be effective antigens[1], and anti-nucleoprotein sera produced in rabbits exhibit a definite cytotoxic activity on the cells of different lines grown in tissue culture[2]. On the other hand, it is generally believed that ribonucleic acid and ribonucleoprotein are instrumental in protein synthesis, and that these cell constituents provide also the patterns for *de novo* production of highly specific proteins, such as immune antibodies. It may be deduced, therefore, that the capacity of antibody-protein formation can be affected by the action of an anti-nucleoprotein serum. The present experiment was done in order to investigate the immunological events which are associated with the activity of anti-ribonucleoprotein and anti-deoxyribonucleoprotein sera.

Ribonucleoprotein-rich fraction[3], 11·0–15·0 mgm./ml. of protein, 45–70 γ/ml. of deoxyribonucleic acid (DNA), and 1,300–1,600 γ/ml. of ribonucleic acid (RNA) and deoxyribonucleoprotein-rich fraction[4] (9·2–11·6 mgm./ml. of protein, 975–1,250 γ/ml. of DNA, and 300–420 γ/ml. of RNA) were isolated from Rhode Island Red chicken organs (spleen, liver and lung). Immune sera were prepared by injecting chicken ribonucleoprotein and deoxyribonucleoprotein into rabbits. Two three-injection series were performed, with an interval of 10 days between them (3 ml. of nucleoprotein per injection subcutaneously). Ten days after the last injection the rabbits were bled and γ-globulin fraction (96·25 mgm./ml. of protein) of anti-ribonucleoprotein serum, and γ-globulin fraction (76·37 mgm./ml. of protein) of anti-deoxyribonucleoprotein serum were prepared as described by Bassett *et al.*[5]. The γ-globulin fraction (89·31 mgm./ml. of protein) of normal rabbit serum was also used in the experiments. Rabbit antisera were investigated for the presence of specific antibodies by diffusion-gel technique and complement fixation[6]. The supernatants obtained by centrifuging at 3,000 r.p.m. for 30 min. chicken nucleoprotein fractions served as antigens. The supernatant of ribonucleoprotein contained 1,915 γ/ml. of protein, 25 γ/ml. of DNA and 450 γ/ml. of RNA, and that one of deoxyribonucleoprotein 2,065 γ/ml. of protein, 900 γ/ml. of DNA and 160 γ/ml. of RNA. Chicken ribonucleic (RNA) and deoxyribonucleic (DNA) acids were also used in complement fixation. In the agar-diffusion reaction a maximum of five zones was observed with

chicken ribonucleoprotein and corresponding antiserum, and four well-defined precipitin lines with chicken deoxyribonucleoprotein and anti-deoxyribonucleoprotein serum. Normal rabbit serum did not react in the agar medium with chicken nucleoproteins. The titres of anti-ribonucleoprotein serum in complement fixation were 0–1/2 with RNA and 1/64–1/128 with ribonucleoprotein, and those of anti-deoxyribonucleoprotein serum were 1/8–1/32 with DNA and 1/16–1/128 with deoxyribonucleoprotein.

Rhode Island Red chickens were divided into three groups: the first group received γ-globulin of anti-ribonucleoprotein serum, the second group γ-globulin of anti-deoxyribonucleoprotein serum, and the third group γ-globulin of normal rabbit serum (control). A first injection (0·3 ml. of corresponding γ-globulin) was given to 6-day-old embryos. The mortality-rates of embryos were 60·7 per cent for the first, 66·7 per cent for the second and 57·2 per cent for the control group. The other four injections were performed on chickens at the age of 32, 35, 38 and 41 days (1 ml. of corresponding γ-globulin per injection intravenously). After a rest of one day, all three groups were injected intravenously with 1 ml. of a 10 per cent suspension of human *O* red cells. Three days later the first group of chickens received the last 1 ml. of anti-ribonucleoprotein, the second group 1 ml. of anti-deoxyribonucleoprotein and the third group 1 ml. of normal rabbit γ-globulin. Seven days after the final injection, the chickens were bled for the first time, and further bleedings were performed every 7 days. A semi-quantitative agglutination reaction was used to test the presence of agglutinins for human *O* red cells in chicken sera.

Table 1. Effect of Rabbit Anti-nucleoprotein Sera on Haemagglutinin Production in Chickens receiving One Injection of Human *O* Red Cells at the Age of 42 Days

| Days after red cell injection | Chickens treated with γ-globulin from anti-deoxyribonucleoprotein serum | | anti-ribonucleoprotein serum | | Normal rabbit serum (control) | |
|---|---|---|---|---|---|---|
| 7 | 7·52 | (10) | 6·47 | (13) | 7·72 | (15) |
| 14 | 6·65 | (9) | 5·86 | (13) | 7·05 | (15) |
| 21 | 6·32 | (8) | 5·23 | (12) | 6·53 | (14) |
| 28 | 5·69 | (8) | 4·65 | (10) | 6·09 | (10) |
| 35 | 4·82 | (8) | 4·43 | (10) | 5·43 | (10) |

The values represent mean peak agglutinin titres ($\log_2$). In parenthesis is the number of chickens tested.

The results are presented in Table 1. The rates of appearance of haemagglutinins in two experimental groups of chickens are similar to the control one. Peak agglutinin titres in the sera of chickens treated with anti-deoxyribonucleoprotein serum were lower than those obtained in control group, but not so low that the difference observed can be considered significant. However, partial suppression of agglutinin production occurred among the chickens injected with anti-ribonucleoprotein serum.

Although the mechanism by which anti-ribonucleoprotein serum causes a decrease in antibody-forming capacity is not clear, it may be postulated that its action is rather at the level of nucleoproteins and cellular membrane (Colter *et al.*[2]). Since the metabolic activity of antibody-forming cells is accompanied by an increased amount of ribonucleic acid[7], it may also be supposed that the anti-ribonucleoprotein serum exhibits an indirect effect on ribonucleic acid, by acting on nucleoproteins which are bound with this nucleic acid. This view seems to be supported by the observation made in the present work, namely, ribonucleic acid scarcely showed antigenic properties, while its protein component reacted rather well with anti-ribonucleoprotein serum. It must be pointed out that the promising results obtained in the present experiments are preliminary ones, and that further investigations are planned in which more specific techniques will be used, including the tissue culture of antibody-producing cells.

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## MICROBIOLOGY

### Formamidase in Mycobacteria and its Use in differentiating Saprophytic Mycobacteria from other Mycobacteria

Recently, biochemical methods have been proposed to differentiate various types of mycobacteria without resorting to their growth characteristics or animal pathogenicity. Thus human tubercle bacilli can be distinguished from all other types of mycobacteria by determining their nicotinic acid production (Konno's niacin test)[1]. Bovine and avian tubercle bacilli would be differentiated from other mycobacteria by determining the activity of nicotinamidase[2] and urease[3], respectively. As for the other types of mycobacteria, namely, unclassified mycobacteria and saprophytic mycobacteria, however, such a reliable method has hitherto not been reported. Bönicke[4] and Kitamura[14] attempted to sub-divide unclassified mycobacteria by the amidase activity of bacterial suspension.

In this communication, we report the occurrence in mycobacteria of an enzyme which catalyses the formation of ammonia from formamide. This enzyme activity was found, among various mycobacteria tested, only in saprophytic mycobacteria. Amidase activity towards formamide has not so far been demonstrated with various preparations, such as rabbit liver, yeast, and *Torula utilis*, and assumed to be non-existent[5]. Halpern and Grossowicz suggested its occurrence in some mycobacteria[6]; but no other report has appeared at present on this enzyme. The natural production of formamide was reported in 1955 as the final product of histidine metabolism in *Aerobacter aerogenes*[7] and *Clostridium tetanomorphum*[8].

Twenty-three strains of various mycobacteria were grown on the surface of Sauton's synthetic liquid medium for 3 weeks (one week for saprophytic mycobacteria). The pellicles were filtered off, and washed four to five times with water. The cells (about 3 gm.

wet weight) were ground in a mortar by hand with equal amount of sea-sand for 30 min. Cell-free extracts were prepared by extracting the paste with five volumes of water for 10 min. and centrifuging at 10,000*g* for 40 min.

The reaction mixture contained 0·5 ml. of the cell-free extracts (approx. 2 mgm. protein), 10 μmoles of formamide, 1·0 ml. of 0·05 *M* phosphate buffer (*p*H 7·0) in a total volume of 2·0 ml. Solutions of enzyme without substrate and substrate alone were used as controls, which were essential. The mixtures were incubated for 4 hr. at 37°. The ammonia formed was determined colorimetrically by Imai's modified procedure[9] of Russel's phenol-hypochlorite method[10].

Among 23 strains tested, the activity of this enzyme was observed only with extracts from saprophytic mycobacteria, as shown in Table 1. With other types of mycobacteria, no activity was detected. Thus, it might be possible to distinguish saprophytic mycobacteria from all other mycobacteria by determining this enzyme activity.

Table 1. Formamidase Activity of Extracts from Various Mycobacteria

| Type | Strain | Activity ($NH_3$ formed, μmoles*) |
|---|---|---|
| Human tubercle bacilli | *H37Rv* | 0 |
| | *H37Rv–INH–R* | 0 |
| | *H37Ra* | 0·2 |
| | *Aoyama B* | 0 |
| Bovine tubercle bacilli | Bovine $D_4$ | 0 |
| | Bovine Miwa | 0 |
| | *BCG* (Japan) | 0 |
| | *BCG–INH–R* | 0 |
| Avian bacilli | 11755 | 0 |
| | 4110 | 0 |
| Unclassified mycobacteria | *P*-1 (Photochromogens) | 0 |
| | *P*-8 (Photochromogens) | 0 |
| | *P*-6 (Scotochromogens) | 0 |
| | 100616 (non-photochromogens) | 0 |
| | Kofu (non-photochromogens) | 0 |
| | *M. fortuitum* | 0 |
| Saprophytic mycobacteria | *M. phlei* | 5·7 |
| | *M. smegmatis* | 7·8 |
| | *M.* 607 | 10·0 |
| | *Asami* | 9·5 |
| | Guinea pig I | 10·1 |
| | Soil III | 7·3 |
| | *M. takeo* | 8·6 |

Substrate, formamide 10 μmoles; *p*H 7·0; incubation at 37° for 4 hr.
* Values are corrected for controls: substrate only and enzyme blank.

Some properties of the enzyme were examined with the preparation from saprophytic *Mycobacterium* 607. This preparation split 79·3 per cent of substrate within 2 hr. under the above assay condition. The rate of the reaction remained constant for more than 2 hr. At a concentration of 5 μmoles formamide per ml. the rate was almost maximum. Dialysis against distilled water had no effect on the activity.

The enzyme solution showed a considerable activity, besides formamide, towards nicotinamide, pyrazinamide, benzamide, *iso*-nicotinamide, L-asparagine, and urea; only weak activity towards L-glutamine, glycinamide, and acetoamide.

The enzyme activity towards formamide was observed over a wide *p*H range (6·0–9·0), with an optimum at *p*H 7·0–8·0. The *p*H activity curve was, though similar to that of nicotinamidase activity, slightly but definitely different from that of benzamidase activity, and markedly different from that of urease activity. This fact seems to suggest that the enzyme might be different from urease, and possibly from benzamidase.

Heating the enzyme solution (*p*H 7·0) at 50° for 10 min. abolished about 80 per cent of the amidase activity towards nicotinamide, pyrazinamide, benzamide, and *iso*-nicotinamide to the same extent; but none of the activities towards formamide, asparagine and urea was impaired. Heating at 60° resulted in complete loss of the aromatic amidase activity as well as asparaginase without affecting the activity towards formamide and urea. (By this heat-treatment, the *p*H curve for formamide was not affected. The enzyme activity was destroyed by heating at 80°. These results render it probable that the enzyme responsible for formamide is not identical with any of these known amidases.

Evidence for this hypothesis was provided by the mixed-substrate method[11]. Further addition of nicotinamide, benzamide, asparagine, or urea to an enzyme system already saturated with formamide increased the rate of ammonia production additively. This indicates that these added substrates are hydrolysed by different enzymes from that concerned with formamide.

Our results seem to indicate that the activity observed towards formamide is due to a new, distinct enzyme which we propose to call 'formamidase'. We are aware that kynurenine formamidase (formylase) is called sometimes by this rather misleading name[11]; but as for this enzyme we think it is more appropriate to call it either 'kynurenine formamidase' as used at present[12] or simply 'formylase' as originally proposed[13]. The name 'formamidase' should be reserved strictly for the enzyme specific for formamide.

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## ENTOMOLOGY

### Resting Habits of *Anopheles gambiae* and *Anopheles pharoensis* in Salt Bush and in Crevices in the Ground

The failure to eradicate *Anopheles gambiae*, the most important vector of malaria in tropical Africa, by spraying the inside of houses with insecticides, had directed attention to the importance of alternative resting places. Box shelters[1] around cattle enclosures

were used to assess the numbers of *A. gambiae* biting cattle during an experiment to break malaria transmission in the Pare-Taveta area of East Africa. Catches in the boxes, in the village of Bumba, showed peaks that corresponded to the dry months June–October, and were thought to be due to the artificial shelters competing favourably against the nearby vegetation as resting places. This is supported by complementary catches in natural resting places outdoors at Bumba between September and June.

Searches, for a total of 333 man/hours, were made in grass, foliage of trees, cacti (*Opuntia* sp.) earth banks, crevices in the ground and salt bush (*Suaeda* sp.) within a radius of three hundred yards of the village, and the mosquitoes collected by sucking tubes. The results are summarized in Table 1. Salt bush and crevices in the ground were the chief sources of *A. gambiae* and were studied in detail; for *Anopheles pharoensis* grass was also an important resting place. The salt bush covered an area of approximately 1,500 sq. yd., stretching along two sides of the village near the huts and cattle enclosures and then beyond for 300 yd. Where the villagers had taken branches for firewood and for enclosure walls, parts of the bush were thin and sparse, but other parts had been left to grow thick to give cover for places used as latrines. The terrain between the village and rice swamps comprised grassland in which deeply creviced patches of bare ground appeared during the dry season, but which were usually absent during the rainy season, November–May. The catches included *A. gambiae* and *A. pharoensis* in all stages of ovarian development, but recently-fed mosquitoes predominated. Precipitin tests on both species, carried out by Mr. B. Weitz, of the Lister Institute, London, showed that specimens from salt bush and crevices in the ground had fed almost entirely on cattle.

Table 1. AVERAGE NUMBER OF *A. gambiae* AND *A. pharoensis* CAUGHT PER MAN/HR. IN DIFFERENT RESTING PLACES

| Resting place | Wet season (November–May) | | Dry season (June–October) | |
|---|---|---|---|---|
| | *A. gambiae* | *A. pharoensis* | *A. gambiae* | *A. pharoensis* |
| Thick salt bush | 3·6 | 0·1 | 0·4 | 0 |
| Thin salt bush | 0·3 | 2·1 | — | — |
| Crevices near village | 0·03 | 0 | 36·6 | 0·5 |

*A. gambiae* was found in greatest numbers in salt bush in which the foliage was dense. The characteristic resting place was in the large salt bushes, on the main branches inside the cavity produced by the arching of the branches as they inclined to the ground. Thin salt bush, either young bushes or new growths from old bushes that had been cut down, was little used as a resting place. In the dry season, dense salt bush lost much of its luxuriant growth and became less suitable as a resting place. Thus the shortage of natural outdoor resting places in the vicinity of the box shelters during the dry season accounted for the seasonal increase in the catches of *A. gambiae* in the boxes. The shortage of outdoor resting places in the dry season was reflected again in the high concentration of *A. gambiae* in a relatively small area of crevieed ground about 300 yd. from the boxes. This finding also shows that there was a seasonal change of resting place depending on the availability of dense salt bush in the wet season and crevices in the dry season.

*A. pharoensis* was quite different in its resting habits and was found in greatest numbers in thin salt bush during the wet season, where it rested on the outer leaves of the vegetation. Small numbers of *A. pharoensis* were found in crevices as well as in grass during the dry season, and it was noted that they rested higher up the crevices than *A. gambiae*.

After establishing that dense salt bush was the principal resting place of *A. gambiae* in the wet season, the bush was cut down at the end of June. Subsequent catches in the box shelters showed that the peak in them was transposed to the wet months[2], thus confirming that, in the absence of nearby natural resting places outdoors, *A. gambiae* entered artificial shelters in large numbers in areas where many cattle were penned outdoors at night.

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## Members of the *Culex pipiens* Series in New Caledonia and the New Hebrides

In 1952–54, during studies of South Pacific mosquitoes and the ecology of their larval habitats, *Culex* (*Culex*) *pipiens fatigans* Wiedemann was recorded from numerous localities[1]. At that time, *C. pipiens australicus* Dobrotworsky and Drummond[2] was known only from Australia. However, this subspecies has since been reported from New Caledonia[3] and the New Hebrides[4], although the latter record is queried in a recent review[5]. Furthermore, another member of Edward's *Culex pipiens* series, *C. iyengari* Mattingly and Rageau, has now been described from the Loyalties and New Caledonia[6].

Accordingly, all specimens identified as *C.p. fatigans* in the account of my investigations[1] have been re-examined. The material still proves referable to this sub-species, with three exceptions, the collection numbers quoted being those of the account referred to:

Collection 2 (in part), ex whaling try pot, Anelgauhat, Aneityum Id., New Hebrides, August 3, 1952.
Collection 49, ex pot hole in rock, Uala, Art Is., Beiep Is., New Caledonia, November 28, 1952.
Collection 56 (in part), ex 44 gallon drum, Poum, northern New Caledonia, December 3, 1952.

All fourth instar larvæ of collection 2 have four pairs of subventral tufts on the siphon, which in most cases tapers most pronouncedly in its distal half, its index being 4·2–4·4. Such larvæ are regarded as undoubted *C.p. fatigans*, although their antennæ are unusually long—0·45–0·52 mm., as compared with a New Caledonian figure of 0·41–0·44 mm. (ref. 3) and 0·41–0·45 mm. in examples from Polynesia (Samoa and Aitutaki) in my own collection. Seven others have an evenly tapered, very slightly curved siphon, its index ranging from 5·8 to 6·2, and their antennæ are 0·55–0·63 mm. long. In all respects other than siphonal curvature, which is characteristic of the Australian type strain of *C.p. australicus*[2], they agree with the New Caledonian larvæ of this sub-species examined by Marks and Rageau[3].

Iyengar's[5] doubt as to the occurrence of *C.p. australicus* in the New Hebrides presumably stemmed from the low siphonal index (4–4·5) given by Rageau and Vervent[4] for their material from Espiritu Santo. The presence of the sub-species in the southern part of the Group, at least, may be due to human agency,

for Anelgauhat was formerly a watering point for ships[7].

Collection 56 includes both *C.p.fatigans* and larvæ in which the siphon has a distinct sinusoidal flexure, an index of 5·0–6·1, and only three pairs of subventral tufts. These features, in combination with the length of the antennæ (0·48–0·52 mm.), identify them as *C. iyengari*[3,8]. All specimens of collection 49 (originally assigned to *C.p. fatigans* with some reluctance[8]) are also referable to *C. iyengari*. This species was previously known from an outlier of New Caledonia, the Isle of Pines, as well as from the mainland and the Loyalty Group. Its range is now extended to the Belep Islands, Art lying as far to the north-west of New Caledonia (approximately 30 miles) as the Isle of Pines does to the south-east.

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## VIROLOGY

### Negative Evidence against Passage of Whole Plant Virus Particles through Gut Wall in Aphid Vectors

In transmission of so-called persistent aphid-borne plant viruses, an incubation period in the insect is generally observed. It is understood that this time is required for the virus circulation in the insect body. Virus taken up with the plant juice is supposed to penetrate the intestinal wall and later the wall of the salivary glands, transport of the virus from the former to the latter being brought about by the blood. This theory is supported strongly by the fact that blood from infective aphids injected into non-infective individuals has been shown to make the latter able to transmit the virus in question. This has been demonstrated for potato leaf roll virus[1–3] and (Ossiannilsson, F., unpublished), beet yellow-net virus[5], and pea enation mosaic virus[4].

Nothing is known, however, about the form in which the virus is thus moving in the body of the vector. From work found in the literature on these matters one is apt to get the impression that the virus is supposed to pass through the insect tissues in the shape of complete molecules, that is, particles like those observed by electron microscope examination of infective plant sap or purified virus preparations. The size of these particles is, however, extremely large, as we know. The molecules of normal protein are very much smaller, but nevertheless the protein has to be broken down by the digestive enzymes before absorption by the mid-gut cells can take place. Since phagocytosis of food particles by the mid-gut cells is unknown in insects[6], a penetration of the intestine wall by intact plant virus particles would be possible only if there existed special pores or ducts through this wall. Results of recent experimental work[7] indicate the presence of capillary leaks of at least 120 Å. radius in the blood-lymph barrier in *Canis*. Analogous conditions might possibly be present in some part of the alimentary canal of aphids. This point does not seem to have been investigated so far, in spite of its significance in the present connexion.

In order to find out whether any such ducts do exist, I have examined the ultrastructure of the wall of the alimentary canal of *Myzus persicae* (Sulzer). These investigations were pursued for two years (1958–60) and concerned four parts of the intestine, namely, the œsophagus, the stomach, the posterior slender part of the mid-gut, and the hind-gut. The aphids were dissected under water, and the parts to be investigated were fixed in osmic acid and embedded in 'Methacrylate'. Thin sections were made by aid of a Philips ultra-microtome and examined in the electron microscope. The results of this work yield a negative answer to the question in point. No ducts whatever through the intestinal wall have been observed, with the exception of tracheoles. It is very difficult to see how the latter could possibly take any part in transport of virus, of course. The intestinal wall is throughout very compact, and a passage of bodies with the dimensions of, for example, 32 × 300 mμ (particles of beet yellow-net virus[5]) through this wall appears to be out of the question. The base membrane of the posterior part of the mid-gut is 0·1–0·3μ in thickness, and no pores could be observed. Moreover, the fore-gut as well as the hind-gut are lined in the interior by a cuticular intima. This is certainly very thin (in the œsophagus $\leq$0·02μ) but devoid of pores visible at a magnification of $\times$27,000. After treating the hind-gut with 10 per cent potassium hydroxide, examination in the electron microscope revealed a reticulate structure of the intima, recalling conditions in the rectal cuticle of *Calliphora*[8], but in this region, too, no open holes or pores could be established.

In work[9] on the ultra-structure of the salivary glands of *Myzus persicae*, Wohlfarth-Bottermann and Moericke established that the basement membrane enclosing these glands, as well as the salivary ducts, has a very dense microstructure, apparently making penetration by virus particles from the hæmocœle into the salivary glands impossible. The conclusion of these authors is that the virus must be assumed to enter the glands in the shape of smaller units. The same conclusion seems to be applicable also for the transport of virus through the wall of the gut, according to the results summarized here.

This work was supported financially by the Swedish Natural Science Research Council.

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# FORTHCOMING EVENTS

*(Meetings marked with an asterisk * are open to the public)*

## Monday, June 26

UNIVERSITY COLLEGE (in the Physiology Theatre, Gower Street, London, W.C.1), at 5 p.m.—Dr. Severo Ochoa (New York University School of Medicine): "Propionic Acid Metabolism in Animal Tissues".*

## Monday, June 26—Wednesday, June 28

NATIONAL PHYSICAL LABORATORY; NATIONAL ENGINEERING LABORATORY; and the BUILDING RESEARCH STATION (at the National Physical Laboratory, Teddington, Middlesex)—Conference on "The Control of Noise".

## Wednesday, June 28

BONE AND TOOTH SOCIETY (at 234 East Portland Street, London, W.1), at 4.15 p.m.—Annual General Meeting, followed by a programme of Casual Communications.

GEOLOGICAL SOCIETY OF LONDON (at Burlington House, Piccadilly, London, W.1), at 5 p.m.—Mr. N. L. Falcon: "Major Earth Flexuring in the Zagros Mountains of South-West Iran"; Dr. M. H. P. Bott: "Geological Interpretation of the Magnetic Anomalies over the Askrigg Block".

MEDICAL RESEARCH COUNCIL (at the National Institute for Medical Research, Mill Hill, London, N.W.7), at 5 p.m.—Dr. Severo Ochoa (New York University School of Medicine): "The Biosynthesis of Ribonucleic Acid".*

# APPOINTMENTS VACANT

APPLICATIONS are invited for the following appointments on or before the dates mentioned:

RESEARCH ASSISTANT IN THE DEPARTMENT OF GEOLOGY, for work on hydrated silicate melts and glasses—Prof. F. W. Shotton, University of Birmingham, Edgbaston, Birmingham 15 (June 28).

ASSISTANT IN THE DEPARTMENTS OF LOGIC AND METAPHYSICS AND MORAL PHILOSOPHY in St. Salvator's College—Joint Clerk to the University Court, College Gate, St. Andrews (June 30).

ASSISTANT LECTURER IN PSYCHOLOGY—The Registrar, The University, Manchester 13 (June 30).

ASSISTANT LECTURER (with a good honours degree or equivalent together with industrial experience, and preferably an interest in research) IN MECHANICAL ENGINEERING—The Clerk to the Governing Body, Battersea College of Technology, London, S.W.11 (June 30).

LECTURER (with experience in electrical measurement or measurement and control) IN ELECTRICAL ENGINEERING—The Secretary, Queen's University, Belfast (June 30).

LECTURER (with experience in the use of digital computers, preferably in applications to crystallography or business calculations) IN THE COMPUTING LABORATORY—The Secretary of University Court, The University, Glasgow (June 30).

ORGANIC CHEMIST (recent graduate, or undergraduate now taking final examinations) IN THE NUTRITION DEPARTMENT, for work on the synthesis of substances of biological interest—The Secretary, Queen Elizabeth College (University of London), Campden Hill Road, London, W.8 (June 30).

RESEARCH ASSISTANTS (2) (with a first- or second-class honours degree in mathematics) IN THE MATHEMATICS DEPARTMENT, to work in one of the following fields: hydrodynamics, elasticity, numerical methods and computing—The Clerk to the Governors, Woolwich Polytechnic, Woolwich, London, S.E.18 (June 30).

SCIENTIFIC ASSISTANT, ABSTRACTOR (with a degree in agriculture or natural science, and able to read Russian)—The Director, Commonwealth Bureau of Pastures and Field Crops, Hurley, Berkshire (June 30).

ASSISTANT LECTURER IN THE DEPARTMENT OF BIOCHEMISTRY—The Dean, St. Thomas's Hospital Medical School, London, S.E.1 (July 1).

JUNIOR RESEARCH FELLOW IN PURE MATHEMATICS—The Registrar, The University, Sheffield (July 1).

RESEARCH ASSISTANT (BIOLOGIST OR CHEMIST), to assist in research on the tank culture of bivalve shellfish at Poole, Dorset, under the supervision of the Professor of Zoology—The Secretary and Registrar, The University, Southampton (July 1).

JUNIOR LECTURER IN ORGANIC CHEMISTRY—The Registrar, Trinity College, Dublin (July 3).

ASSISTANT (with a first- or second-class honours degree in astronomy, mathematics or physics, and preferably an interest in radio astronomy) IN ASTRONOMY—The Secretary of University Court, The University, Glasgow (July 7).

JUNIOR LECTURER IN MATHEMATICS—Prof. E. C. Titchmarsh, Mathematical Institute, The University, 10 Parks Road, Oxford (July 7).

RESEARCH FELLOW (preferably organic chemist with a Ph.D.) IN THE COLLEGE OF SCIENCE AND TECHNOLOGY (DEPARTMENT OF CHEMISTRY), for work in connexion with the development of organic dye filters which will be used for nebular and cometary night-sky photography for astronomical purposes—The Registrar, Manchester College of Science and Technology, Manchester 1 (July 8).

CHAIR OF MICROBIOLOGY in the University of Auckland, New Zealand—The Secretary, Association of Universities of the British Commonwealth, 36 Gordon Square, London, W.C.1 (New Zealand and London, July 15).

LECTURER or ASSISTANT LECTURER (with qualifications in mathematical analysis and/or statistics) IN MATHEMATICS at the University College of the West Indies—The Secretary, Inter-University Council for Higher Education Overseas, 29 Woburn Square, London, W.C.1 (July 17).

ASSISTANT IN RESEARCH (with an honours degree in the natural sciences with chemistry, geology or mineralogy as principal subjects) IN SOIL SCIENCE—The Secretary, School of Agriculture, The University, Cambridge (July 19).

LECTURER or ASSISTANT LECTURER (with a recognized honours degree or equivalent qualification and experience in teaching and research) IN THE DEPARTMENT OF CHEMISTRY, University of Malaya, Kuala Lumpur—The Secretary, Association of Universities of the British Commonwealth, 36 Gordon Square, London, W.C.1 (Kuala Lumpur and London, July 27).

CHAIR OF EDUCATION in Fourah Bay College, The University College of Sierra Leone—The Secretary, Inter-University Council for Higher Education Overseas, 29 Woburn Square, London, W.C.1 (July 31).

CHAIR OF GEOGRAPHY in Fourah Bay College, The University College of Sierra Leone—The Secretary, Inter-University Council for Higher Education Overseas, 29 Woburn Square, London, W.C.1 (July 31).

LECTURER (applied mathematician with experience of numerical analysis and the use of digital computers for the solution of engineering problems) FOR THE NUCLEAR POWER GROUP—Dr. P. J. Grant, Department of Mechanical Engineering, Imperial College of Science and Technology, London, S.W.7 (July 31).

LECTURER IN THE DEPARTMENT OF MINERALOGY AND GEOLOGY, University of Cape Town, South Africa—The Secretary, Association of Universities of the British Commonwealth, 36 Gordon Square, London, W.C.1 (July 31).

READER; a SENIOR FELLOW; and RESEARCH FELLOWS IN THE DEPARTMENT OF NUCLEAR PHYSICS, Institute of Advanced Studies, Australian National University—The Secretary, Association of Universities of the British Commonwealth, 36 Gordon Square, London, W.C.1 (Australia and London, July 31).

READER IN BACTERIOLOGY at St. Bartholomew's Hospital Medical College—The Academic Registrar, University of London, Senate House, London, W.C.1 (July 31).

RESEARCH ASSISTANT (graduate with research experience, an interest in numerical analysis or in some field of the application of numerical computers) IN THE COMPUTING LABORATORY—The Director, University Computing Laboratory, 1 Kensington Terrace, Newcastle upon Tyne 2 (July 31).

SENIOR TECHNICIAN IN THE DEPARTMENT OF ZOOLOGY, University College, Ibadan, Nigeria—The Secretary, Inter-University Council for Higher Education Overseas, 29 Woburn Square, London, W.C.1 (July 31).

FOUNDATION CHAIR OF PURE MATHEMATICS in the School of Mathematics, University of New South Wales, Kensington, New South Wales, Australia—The Agent-General for New South Wales, 56–57 Strand, London, W.C.2 (Australia and London, August 14).

SENIOR LECTURER (with an engineering degree and knowledge and experience of industrial or production engineering, or a science or arts degree with qualifications in statistical methods and operations research) IN INDUSTRIAL ENGINEERING at the University of Melbourne, Australia—The Secretary, Association of Universities of the British Commonwealth, 36 Gordon Square, London, W.C.1 (Australia and London, August 31).

ASSISTANT, Grade B (honours graduate, preferably with teaching or research experience), IN MATHEMATICS; and an ASSISTANT, Grade B (honours graduate, preferably with teaching or research experience), IN GEOLOGY—The Principal, Kingston Technical College, Fassett Road, Kingston-upon-Thames.

CHEMIST or BIOCHEMIST (with a first- or second-class honours degree) IN THE RADIOBIOCHEMISTRY DEPARTMENT, to join a small team working on the metabolism of fat in the ruminant, and in particular involves a study of the biochemical forms of radioactivity in blood, milk and various organs after the administration of labelled lipids—The Secretary, National Institute for Research in Dairying, Shinfield, Reading, quoting Ref. No. 61/20.

GRADUATE RESEARCH ASSISTANT IN THE DEPARTMENT OF BIOLOGY AND GEOLOGY, to work in a team engaged on a survey of marine plankton—The Principal, Norwood Technical College, Knight's Hill, London, S.E.27, quoting Ref. FE.3/N/1553/6.

LECTURER or ASSISTANT LECTURER (with qualifications in mathematical analysis and/or statistics) IN MATHEMATICS at the University College of the West Indies—The Secretary, Inter-University Council for Higher Education Overseas, 29 Woburn Square, London, W.C.1.

LECTURER (with teaching experience and preferably qualified to undertake some teaching of biology) IN PHYSIOLOGY—The Clerk to the Governing Body, Battersea College of Technology, London, S.W.11.

PRINCIPAL SCIENTIFIC OFFICER (with training in physiology and/or biochemistry, and preferably also in physics and experience in work on blood) (Ref. 61/18), and an ASSISTANT EXPERIMENTAL OFFICER (preferably with a pass degree or equivalent and experience in biological work) (Ref. 61/19), for work on the flow and coagulation of blood—The Secretary, National Institute for Research in Dairying, Shinfield, Reading, quoting appropriate Ref. No.

RESEARCH STUDENTS (with, or anticipating to have, a good honours degree in chemistry, Grad.R.I.C., or Dip.Tech. in chemistry) IN THE DEPARTMENT OF PURE AND APPLIED CHEMISTRY; research topics will be selected from the following fields: the chemistry and origin of coal tar constituents; low temperature carbonization studies; physicochemical studies, including electrochemistry, surface chemistry, and states of aggregation in solution—Head, Chemistry Department, Northampton College of Advanced Technology, St. John Street, London, E.C.1.

SENIOR ASSISTANT (with physics and/or mathematics to degree standard and some secretarial experience), for work which will include preparation of material for publication, correspondence in connexion with publications, a small amount of committee work and responsibility for day to day running of the office; and an EDITORIAL ASSISTANT (with physics and/or mathematics to degree standard, and preferably able to type), to assist in the preparation of material for publication—The Editor and Deputy Secretary, Institute of Physics and the Physical Society, 1 Lowther Gardens, London, S.W.7.

SENIOR LECTURERS AND LECTURERS IN APPLIED PSYCHOLOGY (PSYCHOMETRICS AND EXPERIMENTAL PSYCHOLOGY); BOTANY; MATHEMATICS; and PHYSICS in the Faculty of Science, University

of New South Wales, Australia—The Agent-General for New South Wales, 56–57 Strand, London, W.C.2, and The Appointments Section, University of New South Wales, Box 1, Post Office, Kensington, N.S.W., Australia, quoting Ref. SA1.

TECHNICIAN IN THE RESEARCH LABORATORY, to assist in the preparation of material for human chromosome studies—The Administrative Officer, Mount Vernon Hospital, Northwood, Middlesex.

# REPORTS and other PUBLICATIONS

*(not included in the monthly Books Supplement)*

## Great Britain and Ireland

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Further details of the activities of the Laboratory and conditions of appointment may be obtained from the Agent-General for New South Wales, 56-57 Strand, London, W.C.2, with whom four copies of applications should be lodged, together with the names of three referees and a recent photograph, and a copy forwarded to the Appointments Section, the University of New South Wales, P.O. Box 1, Kensington, N.S.W., by airmail to arrive before August 31, 1961.

### UNIVERSITY OF CAMBRIDGE
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Applications are invited for the post of Assistant in Research in Soil Science. Applicants should hold an honours degree in the natural sciences with chemistry, geology or mineralogy as principal subjects. The successful candidate will be expected to engage in the current research programme of the Department, particulars of which are obtainable from the address given below. The post is pensionable and the salary is £750 a year rising by annual increments of £50 to a maximum of £1,000. Age, qualifications and experience will be taken into account in determining the initial salary. A non-pensionable payment of £50 a year is made for each dependent child who is under 16 or in receipt of full-time education. A limited contribution may be made toward the removal expenses of the successful candidate.

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(No. 464/233) (Several Positions)

The Organization's **Division of Textile Industry, Geelong, Victoria,** invites applications for research positions from honours graduates in science, or engineering with some years post-graduate research experience.

The Division, one of three constituting the Wool Research Laboratories, is broadly concerned with development of new physical and chemical techniques in wool textile processing and provides well-equipped laboratories for fundamental studies and full scale mill equipment for application of results. The wide field of research includes absorption studies on wool, fibre friction, permanent setting, shrinkage prevention, mechanical action of machines on wool fibres, servo-control mechanisms in processing and development of new machines.

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(ii) The development of new physical methods for separating vegetable material from wool;
(iii) Physical studies on fibre friction, and the effects of lubricants;
(iv) Investigation of new methods of yarn production;
(v) Fibre behaviour in processing using radioactive and high speed photographic techniques.

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(No. 464/232)

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South African Scientific Liaison Office,
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Applications should reach the Director, National Building Research Institute, P.O. Box 395, Pretoria, South Africa, from whom further information can be obtained, not later than August 31, 1961.

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*Salary Scales:* **RESEARCH FELLOWS:** £700 to £1,150 with training and graduate allowances where applicable. Further details can be given on the basis of the applicant's biographical data. As an indication, it may be noted that an applicant with a good honours degree, or a Ph.D. gained as the result of five years' approved full-time study would have a starting salary of about £955.

**RESEARCH ASSISTANTS:** £600 to £650.

*Further particulars and forms of application from the Bursar, College of Advanced Technology, Gosta Green, Birmingham, 4. Applications to be received within 14 days of this advertisement. Please quote 561/D.*

K. R. PILLING, Clerk to the Governors

## JENSON & NICHOLSON LIMITED
## ROBBIALAC COLORIZER PAINTS

require several

## SCIENCE GRADUATES

**to join their Production and Research and Development Laboratories at Stratford, London, E.15.**

**Applications are invited from Graduates who have had experience in the Paint Industry, but applications from Students Graduating this year will be considered.**

**A good Starting Salary is offered commensurate with qualifications and experience and the posts afford ample opportunity for progress.**

**Please write, giving full particulars and quoting Ref. A.13, to:**

The Personnel Manager,
Jenson & Nicholson Limited,
Jenson House, Carpenters Road,
Stratford, London, E.15

## ATOMIC ENERGY RESEARCH ESTABLISHMENT

HARWELL

requires an

### APPLIED MATHEMATICIAN

for work covering the reactor physics aspects of research reactors, and to lead a team associated with

1. Design studies on possible new research reactors.
2. Theoretical analysis and interpretation of experimental results obtained in the existing research reactors or the zero energy reactor DAPHNE.
3. Theoretical support work, e.g., mathematical problems associated with Wigner Energy Release.

Basic theoretical work on reactors will be encouraged. The Establishment at present has a Mercury Computer and has direct access to the IBM 709 and 7090.

Salary: £1,840 to £2,590 per annum.

A first- or good second-class honours degree is essential, together with substantial relevant experience.

Housing and contributory pension schemes.

Send Postcard for details to Personnel Manager (1975/34), A.E.R.E., Harwell, Didcot, Berks.

## AUSTRALIAN NATIONAL UNIVERSITY

INSTITUTE OF ADVANCED STUDIES
DEPARTMENT OF NUCLEAR PHYSICS

The University proposes to make a number of appointments in the Department of Nuclear Physics (Head of Department: Professor E. W. Titterton, C.M.G., F.A.A.). The posts available are: Readership, not less than £A.3,250; Senior Fellowship, £A.3,000 to £A.3,550; Research Fellowships, £A.1,625 to £A.2,450. The Department is well equipped with a 12 MeV. Tandem electrostatic accelerator, a 2 MeV. Van der Graaf generator, a 1.2 MeV. Cockcroft Walton machine and a 33 MeV. electron synchrotron. Two precision particle spectrometers, a Buechner spectrograph, crystal, solid state, gas and emulsion detectors with associated multichannel recording equipment are available for use with these machines. The main fields of work are in nuclear photodisintegration and its inverse processes and in nuclear structure studies. Superannuation is on the F.S.S.U. pattern. Reasonable travel expenses are paid, and assistance with housing is provided. In addition to the posts referred to above, a number of scholarships are available for men who have completed a M.Sc. degree or who have had outstanding results in their honours B.Sc. examinations. The scholarships are tenable for two or three years and the basic allowance is £A.925 per annum; married scholars with dependent children may be granted an additional allowance of £A.265 per annum in respect of the first child and a further £A.80 per annum for each other child. A contribution towards fares is paid.

Further details are available from the Secretary, Association of Universities of the British Commonwealth, 36 Gordon Square, London, W.C.1. Applications close, in Australia and London, on July 31, 1961.

## BIRKENHEAD EDUCATION COMMITTEE

BIRKENHEAD TECHNICAL COLLEGE

Applications are invited for the following appointments to the full-time staff:

CHEMICAL ENGINEERING DEPARTMENT

(a) Lecturer in Chemical Engineering subjects to A.M.I.Chem.E. standard.

SCIENCE DEPARTMENT

(b) Lecturer in Physical Chemistry. (c) Assistant Grade B in Inorganic Chemistry.

Salary in accordance with the Burnham Technical Scale.

Further particulars and forms of application may be obtained from the undersigned, to whom completed applications should be returned by July 7, 1961.

H. GLYN WILKINSON,
Director of Education.

Education Offices,
63 Hamilton Square, Birkenhead.

## LANCHESTER COLLEGE OF TECHNOLOGY

COVENTRY

Principal: A. J. Richmond, B.Sc.(Eng.), Ph.D., M.I.Mech.E.

DEPARTMENT OF AERONAUTICAL ENGINEERING

Head of Department: H. G. Cuming, M.A., Ph.D., D.I.C.

SENIOR LECTURER IN AIRCRAFT STRUCTURES

Applications invited for above new post in rapidly expanding department. Candidates should normally be University graduates and have had industrial and/or research experience. Staff accommodation and classrooms are in new building opened last year and entirely new laboratories will be available in 1963. These will be equipped to the highest modern standards. Full-time staff are encouraged to undertake research work and the successful candidate will be expected to make a substantial contribution towards the development of the new Structures Laboratory and undertake a correspondingly reduced amount of class teaching for the time being. A Dip.Tech. (Eng.) course in Aeronautical Engineering is approved and will commence in September, 1961. Salary (now under review): £1,550 by £50 to £1,750 per annum. In certain circumstances persons appointed may be paid commencing salary above minimum of scale.

Further particulars and application forms from the Registrar, Lanchester College of Technology, Priory Street, Coventry, to whom completed forms should be returned by June 29.

W. L. CHINN,
Director of Education.

## BATTERSEA COLLEGE OF TECHNOLOGY

LONDON, S.W.11

Applications are invited from graduates of a British University for the post of Senior Lecturer in Biochemistry entailing participation in the planning of a proposed course for a Diploma in Technology in Microbiology, and of postgraduate courses. Applicants should be of good standing in their research field, and will be encouraged to continue with research. Salary scale: £1,588 to £1,801, less statutory deductions.

Further particulars from the Clerk to the Governing Body, to whom applications should be sent as soon as possible.

## BATTERSEA COLLEGE OF TECHNOLOGY

LONDON, S.W.11

Applications are invited from graduates of a British University for the post of Lecturer in Physiology in the Department of Health Education. Candidates should have had teaching experience and, preferably, should be qualified to undertake some teaching of biology. The successful candidate will be encouraged to undertake research for which appropriate relaxation will be granted. Salary £1,408 by £35 to £1,601.

Further particulars from the Clerk to the Governing Body, to whom applications should be sent as soon as possible.

WORKS CHEMIST. A VACANCY OCCURS at the Extraction Plant of the Pyrethrum Board of Kenya at Nakuru for a Works Chemist. The duties will be chiefly analytical control but participation in factory operations is also included. The appointment is open to male candidates, who should possess a degree in chemistry or the equivalent Higher National Certificate in chemistry would be considered where the applicant has had approved experience. Salary: £1,400 by £50 to £1,750. The contract would be initially for a tour of three or four years, and subject to renewal. Return air fares paid up to three adult passages. Flat or house, with hard furnishings, available at a rental of not more than 15 per cent of salary with a maximum of £150 per annum. Provident Fund contribution of 5 per cent of salary, plus 10 per cent contribution by the Board. Medical and hospital benefits are offered, the Board paying two-thirds of the premium. Annual local leave of eighteen days is granted, with three or four months overseas leave at the end of the tour. Nakuru is in the Kenya Highlands amidst fine scenery, at an altitude of 6,000 ft., and has a pleasant, temperate climate. The Board's factory is for the solvent extraction of pyrethrum flowers, and is now being increased to treble its original capacity (1959) as a result of the rapid expansion of the Overseas market.—Applications, giving full details of age, education, qualifications and experience, etc., should be sent to the African Pyrethrum Technical Information Centre, 216 Grand Buildings, Trafalgar Square, London, W.C.2.

AIC **Executive Selection Division**

*is advising on the following appointment*

## TECHNICAL DIRECTOR
## High Vacuum Engineering

for a Company in the North Midlands making vacuum equipment. The Technical Director will be required to supervise the design of special high vacuum equipment to customers' requirements. He will have to be a commercially minded man as well as an engineer. A very high salary will be offered. (Mr. A. J. C. Lyddon.)

*Brief written applications should be sent, in complete confidence, to the Consultant concerned at:*

ASSOCIATED INDUSTRIAL CONSULTANTS LIMITED,
BUSH HOUSE, LONDON, W.C.2.

**Associated Industrial Consultants**

SHELL **Shell Chemicals**

## STATISTICS IN RESEARCH AND DEVELOPMENT

Carrington Research Laboratory (near Manchester) has a vacancy for a

## GRADUATE

interested in the application of statistical methods in all phases of its operations. The work covers the design of experiments and the interpretation of results, the optimisation of process conditions, and the control of chemical, physical, and mechanical testing procedures.

Men or women candidates should be under 30 years of age and have a degree in:

either (a) **CHEMISTRY or CHEMICAL ENGINEERING and research experience in these fields, with a subsequent qualification in statistics or experience in the use of statistical methods.**

or (b) **MATHEMATICS or STATISTICS with a real interest in the application of statistical methods in research and production.**

Salary based on qualifications and experience. Excellent Pension Scheme and other benefits.

Applications (quoting Ref. CRL.133) to:

**SHELL CHEMICAL COMPANY LIMITED,**
**Personnel Department, 29 Old Burlington Street, London, W.1.**

## *DEVELOPMENT SCIENTISTS*
## *FOOD PRODUCTS*

BEECHAM FOODS LIMITED have interesting vacancies in Gloucestershire, Hertfordshire, and Brentford for science graduates in their expanding Product Research Division. These posts cover a widely varying field of food technology and both newly qualified and experienced Scientists aged 20-35 will be considered for appointment.

It is desirable that those with experience have worked in one or more of the following fields: carbonated drinks, fruit juices, essences, processing and preservation of fruits and vegetables. An ability to accept managerial responsibility will aid prospects of promotion.

The appointments qualify for the Company's non-contributory pension/life assurance and profit participation schemes.

*Applications should be addressed to the*
**Personnel Manager, ref. D/C,**
**Beecham House, Brentford, Middx.**

## NIGERIAN COLLEGE OF TECHNOLOGY

ZARIA

FACULTY OF ENGINEERING OF UNIVERSITY COLLEGE, IBADAN

Applications are invited for a Lectureship or Senior Lectureship in Civil Engineering. Candidates should have a good honours degree, and should preferably be corporate members of the Institution of Civil Engineers. Teaching and research experience are desirable. Candidates should have a special interest in one or more of the following: Geology, Surveying, and Soil Mechanics. Students at the College are at present working for the degree of B.Sc.(Eng.) of the University of London in special relation. Salary scales (contract): Lecturers, £1,500 by £75 to £2,400 per annum; Senior Lecturers, £2,475 by £90 to £2,745 per annum, plus car allowance of £14 15s. a month and existing F.S.S.U. contributions or a tax free gratuity of £150 per annum. Free passages (up to a maximum of four adult passages) on appointment, termination, and annual leave in U.K. Part-furnished quarters at low rental. Children's U.K. maintenance and other allowances. Appointments normally on contract for two sessions in first instance and renewable.

Detailed applications (eight copies), naming three referees, as soon as possible, to Secretary, Inter-University Council for Higher Education Overseas, 29 Woburn Square, London, W.C.1, from whom further particulars may be obtained.

## ESSEX

SOUTH-WEST ESSEX TECHNICAL COLLEGE FOREST ROAD, WALTHAMSTOW, E.17

Required September 1, or as soon as possible afterwards: (1) Lecturer in Organic Chemistry, to teach students to B.Sc. General, H.N.C., and Grad.R.I.C. Candidates should hold an honours degree or G.R.I.C., and should have teaching experience. Higher degrees and specialization in a branch of organic chemistry are additional recommendations. (2) Lecturer in Inorganic Chemistry to teach students to B.Sc. General, and Grad.R.I.C. Candidates should hold an honours degree or G.R.I.C., and should have teaching experience. Higher degrees and specialization in a branch of inorganic chemistry, radio chemistry, or chemical instrumentation, are additional recommendations. (3) Assistant Lecturer (Grade B) to teach Chemistry mainly to G.C.E. Advanced students, but also to B.Sc. (Part I) and H.N.C. students. Candidates should hold an honours degree or G.R.I.C. Higher degrees and teaching experience are additional recommendations. In respect of these appointments, research for which considerable facilities are available, will be encouraged. Salaries within scales: Lecturer, £1,370 to £1,550 per annum; Grade B, £700 to £1,150 per annum, both plus London allowance of £38 or £51 per annum. In respect of the Grade B post, additions to scale salary are also payable for approved training and graduate qualifications.

Applications (no forms) to the Principal, giving the names and addresses of three referees.

## MANCHESTER COLLEGE OF SCIENCE AND TECHNOLOGY

(Faculty of Technology in the University of Manchester)

Applications are invited for Lectureships, an Assistant Lectureship and a Demonstratorship in the Department of Mathematics in the College, with corresponding title and status in the University of Manchester. Members of staff are expected to lecture to students taking degrees in mathematics and other subjects, and to take an active part in the expansion of research work in the department in mathematics, applied mathematics and statistics. Salary: Lecturer, £1,050 to £1,850 per annum. Assistant Lecturer, £800 to £950 per annum, Demonstrator, £675 to £700 per annum. F.S.S.U. and family allowances.

Further information and form of application may be obtained from the Registrar, the Manchester College of Science and Technology, Manchester 1, to whom completed forms should be returned by Friday, June 30, 1961.

A SENIOR TECHNICIAN AND A TECHNICIAN (N.H.S. salary scales) are required by the Regional Steroid Laboratory, Royal Infirmary, Glasgow. The Laboratory is concerned with special analyses of steroids in body fluids. Experience in chromatographic and isotopic techniques would be an advantage.—Applications, giving details of age, qualifications and previous experience, together with the names of two referees, should be addressed to the Secretary and Treasurer, Board of Management for Glasgow Royal Infirmary, 84 Castle Street, Glasgow, C.4, from whom further details may be obtained.

## AUSTRALIA

### COMMONWEALTH SCIENTIFIC AND INDUSTRIAL RESEARCH ORGANIZATION

### *Insect Ecologist and Insect Physiologist for Research on Pasture Insects*

The Organization's **Division of Entomology, Canberra, A.C.T.**, proposes to establish a research team consisting of an Insect Ecologist and an Insect Physiologist, to investigate the ecology of certain complexes of soil-inhabiting pasture insects native to Eastern Australia. A plant ecologist will co-operate with the team to study the nature of the environmental changes brought about by pasture improvement operations that allow such insects—notably cockchafers and underground grass grubs—to become serious pests. The ultimate aim is to determine what combinations of cultural and control practices will lead to maximum pasture productivity in a particular region.

### INSECT ECOLOGIST

(No. 180/183)

The successful applicant, who should be an Honours graduate in Science (or equivalent qualifications) with some years postgraduate training and/or experience in field ecological research, will be stationed at Armidale, N.S.W., and will be responsible for co-ordinating the work of the team.

### INSECT PHYSIOLOGIST

(No. 180/184)

Applicants should have similar qualifications as the Insect Ecologist with postgraduate training and/or experience which, with advantage, would lie in the field of sensory physiology. He will be particularly concerned with the attraction and feeding responses of the insects which lead to their preferential attack on desirable introduced plant species, which also involves a study of larval nutrition. He will be stationed initially at Canberra, A.C.T., where a full range of facilities for physiological and biochemical research are available, but would spend such time in the field as the investigation required.

**Salary: Dependent on qualifications and experience within the ranges: £A.1,510 to £A.2,265 per annum or £A.2,395 to £A.2,720 per annum.**

**Salary for women will be £A.180 per annum less than corresponding rates for men.**

**Promotion within C.S.I.R.O. is by merit and may ultimately go beyond the upper limit of the scale within which the original appointment is made.**

**Fares paid. Further particulars of conditions, etc., supplied on application to:**

**Mr. E. J. Drake, Chief Scientific Liaison Officer, Australian Scientific Liaison Office, Africa House, Kingsway, London, W.C.2.**

**to whom applications (quoting appropriate appointment number) should be addressed by July 29, 1961.**

## UNIVERSITY OF BIRMINGHAM

DEPARTMENT OF PHYSICS

Applications are invited for Research Fellowships financed under a D.S.I.R. grant for bubble chamber track analysis. Fellows will participate under the direction of Dr. L. Riddiford and Professor W. E. Burcham, in a nationally organized programme of measurement and analysis of bubble chamber photographs, particularly those to be obtained from the CERN proton synchrotron, Geneva, with the British National Bubble Chamber. Applications should have experience of research in Physics, though not necessarily in this particular field. Appointments, which carry F.S.S.U. and Family Allowance benefits, will be in the range £800 to £900; initial stipends being related to qualifications and experience.

Applications (three copies), naming two referees, should be sent as soon as possible to the Assistant Registrar (Science), The University, Edgbaston, Birmingham, 15, from whom further particulars can be obtained.

## GOVERNMENT OF TANGANYIKA

MINERALOGIST

Qualifications and duties: A good honours degree in geology, with emphasis on mineralogy, and preferably with experience of spectrograph and X-ray apparatus. The appointee would be engaged on the identification of minerals and would be required to do some field work. Age: Preferably under 35. Terms of appointment: On contract for one or two tours of 21-27 months with salary, according to experience, in the scale £1,266 to £2,448 plus a gratuity of 25 per cent. Free passages. Generous education allowances. Government quarters at rental if available. Free medical attention. Generous leave.

Apply to Director of Recruitment, Colonial Office, London, S.W.1, stating full name, age, qualifications and experience and quoting C1/BCD105/8/04.

## CITY OF LIVERPOOL EDUCATION COMMITTEE

COLLEGE OF TECHNOLOGY

Principal: S. A. J. Parsons, B.Sc.(Econ.), M.I.Mech.E., M.I.Prod.E., M.B.I.M.

Applications are invited for the appointment of Lecturer in Mathematics (full-time). Salary, £1,370 by £35 to £1,550 per annum (Burnham Technical Report). Commencing salary may be assessed according to previous industrial or professional experience. Applicants should have an honours degree and preferably have had teaching and/or industrial experience, the capacity to develop postgraduate work and research is desirable. This is a new appointment due to the expansion of the mathematical section of the department particularly in connection with Numerical Analysis and Statistics.

Application form (returnable by June 30, 1961), and further particulars from H. S. Magnay, M.A., Director of Education, 14 Sir Thomas Street, Liverpool 1.

THOMAS ALKER,
Town Clerk and Clerk to the Local Education Authority. (J.6870)

## UNIVERSITY OF SOUTHAMPTON

PHYSICS DEPARTMENT

Applications are invited for Research Fellowships and Studentships to work in the surface physics group. The work, which is sponsored by the Atomic Energy Research Establishment, will involve the application of ultra-high vacuum, photoelectric and work function techniques to investigations with low work function surfaces. The fellowships, valued at £900 per annum and tenable for two years, will include F.S.S.U. benefits. The studentships, which may lead to a higher degree, are valued up to £415 per annum together with demonstrating fees.

Applications, quoting two referees, should be sent to the Secretary and Registrar, the University, Southampton, not later than August 1, 1961.

## UNIVERSITY OF MELBOURNE

LECTURER OR SENIOR LECTURER IN ZOOLOGY

Applications are invited for the above-mentioned position. It is desirable that applicants should be able to take up the position by March, 1962. Teaching duties would include lecturing to one section of the first year biology class and some responsibility for laboratory work, together with some advanced teaching in the successful applicant's own field or fields of interest. Other things being equal, preference will be given to candidates whose research is in the field of ultra-structure biology. The Zoology and Botany Departments will jointly operate a high resolution electron microscope which will be installed in 1962. The salary ranges are: Lectureship, £A.1,660 to £A.2,360 per annum; Senior Lectureship, £A.2,480 to £A.2,950 per annum. Initial salary will be determined according to qualifications and experience. Superannuation is on the F.S.S.U. basis.

Further particulars and conditions of appointment may be obtained from the Secretary, Association of Universities of the British Commonwealth, 36 Gordon Square, London, W.C.1. Applications close, in Australia and London, on July 31, 1961.

## ESSEX

SOUTH-WEST ESSEX TECHNICAL COLLEGE AND SCHOOL OF ART
FOREST ROAD, WALTHAMSTOW, E.17

Senior Lecturer in Physical-organic Chemistry required as soon as possible. The person appointed will assist in the General Teaching of Organic Chemistry to H.N.C., B.Sc. General, Grad.R.I.C., and Laboratory Technician courses, and will be responsible for the teaching of special subjects, including ion exchange in the special and posteraduate courses. Experience in the field of protein chemistry, nucleic acid chemistry, the application of X-ray measurements to chemical problems, or interest in electronic instrumentation is an added recommendation. Candidates should have teaching experience, high academic qualifications and evidence of research ability. Salary within scale £1,550 to £1,750 per annum, plus London allowance of £38 or £51 per annum.

Apply by letter (no forms) to Principal, giving the names and addresses of three referees.

## UNIVERSITY OF GLASGOW

RESEARCH FELLOWSHIP IN THE COMPUTING LABORATORY

Applications are invited for the post of Research Fellow in the Computing Laboratory, tenable from October 1, 1961. Applicants should have an honours degree in mathematics or a related subject. Experience in the use of digital computers, although not necessary, would be an advantage. The Fellow will be required to undertake research in mathematical fairing of ship's lines. The salary, depending on qualifications and experience, will be not more than £1,500 per annum.

Applications (three copies), giving the names of not more than three referees, should be lodged, not later than June 30, 1961, with the undersigned, from whom further particulars may be obtained.

ROBT. T. HUTCHESON,
Secretary of University Court.

## IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY

CHEMISTRY DEPARTMENT

Two Research Assistantships are available for work with Professor R. M. Barrer on the physical and hydrothermal chemistry of soil-forming minerals; the senior post at £900 by £50 to £1,100 plus F.S.S.U. and family allowances; the junior post at £450 by £50 to £650.

Applications, giving details of academic background and names of referees, should be sent to Professor R. M. Barrer, F.R.S., Chemistry Department, Imperial College, London, S.W.7.

## BATTERSEA COLLEGE OF TECHNOLOGY

LONDON, S.W.11

Applications are invited for the post of Assistant Lecturer in Microbiology in the Department of Health Education. Candidates should possess a recognized qualification, preference being given to those with a knowledge of elementary virology and/or micology and with some teaching experience. The successful candidate will be encouraged to undertake research, for which appropriate relaxation will be granted. Salary within the range of £950 to £1,486.

Further particulars from the Clerk to the Governing Body, to whom applications should be sent as soon as possible.

## COLLEGE OF ADVANCED TECHNOLOGY, BIRMINGHAM

*Applications are invited for the following posts:*

### DEPARTMENT OF ELECTRICAL ENGINEERING

**RESEARCH FELLOW** in new semi-conductors, and dielectrics, development of new magnetic materials and annealing processes or in the field of control engineering.

**RESEARCH ASSISTANTS** in new semi-conductors, insulators, new magnetic materials, control engineering measurements, new instruments.

### DEPARTMENT OF MECHANICAL ENGINEERING

**RESEARCH FELLOW** in Metal deformation, Plasticity, Air lubricated bearings, or Shaft Vibrations and Whirling.

**RESEARCH ASSISTANTS** in Whirling and Vibrations of shafts, or metal deformation and plasticity.

### DEPARTMENT OF PRODUCTION ENGINEERING

**RESEARCH FELLOW & RESEARCH ASSISTANT**

in Machine Tools and/or Metrology, or related areas.

Candidates for Research Fellowships must either have shown exceptional promise in research in science or technology, or in industrial experience relevant to the proposed subject for research. They should possess a good first degree, and a higher degree gained as the result of research work; or possess a college associateship or Diploma in Technology or appropriate professional qualification followed by exceptionally valuable and interesting industrial experience, or appropriate research work in industry, research associations, or Government establishments. Candidates should submit their own research proposals for consideration. The appointment will be normally tenable for three but not more than four years.

Candidates for Research Assistantships should possess a Diploma in Technology, a university degree or equivalent qualification. The research work carried out may normally be submitted for a higher degree or other appropriate alternative higher qualification. The appointment will normally be tenable for two years but may be renewed for not more than one further year.

*Salary Scales:* **RESEARCH FELLOWS:** £700 to £1,150 with graduate and training allowances where applicable. Further details can be given on the basis of the applicant's biographical data. As an indication, it may be noted that an applicant with a good honours degree or a Ph.D. gained as the result of five years' approved full-time study would have a starting salary of about £955.

**RESEARCH ASSISTANTS:** £600 to £650.

*Further particulars and forms of application from the Bursar, College of Advanced Technology, Gosta Green, Birmingham, 4. Applications to be received within 14 days of this advertisement. Please quote 161/D.*

**K. R. PILLING, Clerk to the Governors**

## BRITISH TITAN PRODUCTS COMPANY LIMITED

RESEARCH STUDENTSHIP IN INORGANIC CHEMISTRY

Applications are invited for the above studentship, which will become vacant on October 1, 1961. Candidates will be expected to conduct independent research in some branch of inorganic chemistry. They should be normally resident in the U.K. and be British subjects. They should have completed the degree of Ph.D. The emolument will be £850 per annum, subject to income tax. No marriage or family allowances will be paid. The selected candidate will be allowed to do up to six hours teaching a week and to receive payment for this.

Applications should be submitted as soon as possible and not later than July 15, 1961, to Professor H. J. Emeléus, at the University Chemical Laboratory, Lensfield Road, Cambridge, from whom further particulars may be obtained.

A VACANCY EXISTS FOR AN INVESTIGATOR to work in a team studying dust problems in the ceramic industry. Applicants should have some scientific or technological qualifications and experience either of the ceramic industry or of dust investigation techniques.—Applications, with details of age, qualifications and experience to the Director of Research, Dr. N. F. Astbury, the British Ceramic Research Association, Queens Road, Penkhull, Stoke on Trent.

## UNIVERSITY COLLEGE OF SOUTH WALES AND MONMOUTHSHIRE

Applications are invited from graduates in mathematics or physics for a Research Associate to perform theoretical work on semiconductors, as a member of a small group in the department of Applied Mathematics. The appointment will be for a period of three years in the first place, and will carry a salary of up to £1,000 per annum, depending on age and qualifications. A small travelling allowance is also available.

Applications (including the names of two referees), should reach Professor P. T. Landsberg, Department of Applied Mathematics, University College, Cardiff, Wales, as soon as possible, and not later than July 20, 1961.

B.B.C. REQUIRES AN ENGINEER (BRITISH Subjects only) for their Research Department, Kingswood Warren, Surrey. Applicants should have a degree in physics or electrical engineering and an interest in research. A knowledge of and interest in music and high-quality sound reproduction would be an advantage. The work will include the testing of sound and television studios and research in a wide field embracing acoustics, sound insulation and noise reduction. Salary is in the scale of £1,230 to £1,780 per annum according to qualifications and experience.—Write for application form to Engineering Recruitment Officer, Broadcasting House, London, W.1, quoting reference 61.E.132.N.

## THE CARBORUNDUM COMPANY LIMITED

**requires a**

# QUALITY CONTROL STATISTICIAN

in its Technical Branch at Trafford Park, Manchester

The duties will include devising and introducing statistical methods in the various manufacturing Divisions of the Company. A degree in mathematics and/or good qualifications in statistics are essential. Practical experience in the application of statistical control methods would be an advantage.

All applications, which will be treated in strict confidence, should include details of age, qualifications and experience (if any) and addressed to :

**The Personnel Officer,**
**The Carborundum Company Limited,**
**Trafford Park, Manchester 17**


## UNIVERSITY OF QUEENSLAND

### READER AND SENIOR LECTURER IN ELECTRICAL ENGINEERING

The University invites applications for two posts in the Electronics and Communications Section of the Department of Electrical Engineering.

Reader: Salary £A.2,960 by £A.60 to £A.3,200. Applicants are required to have a higher degree in electrical engineering and experience in some aspect of electronics or communications. The successful applicant is required to take charge of the electronics and communications section of the Department of Electrical Engineering under the general direction of the Professor of Electrical Engineering. Evidence should be submitted of experience in lecturing on theoretical topics to honours students and of ability to supervise and participate in research projects.

Senior Lecturer: Salary £A.2,520 by £A.70 to £A.2,870. Applicants must hold an honours degree in electrical engineering, with specialization in electronics. The duties will include lectures on advanced topics in the field of electronics and arrangement of the appropriate practical work. Participation in the research work of the Department is expected.

The University has recently planned a Computer Centre and a G.E. 225 computer is expected to be in operation within one year. The successful applicants will be entitled to participate in the benefits available to the Academic staff which include F.S.S.U. type Superannuation, Housing Assistance, Study Leave and Travel Grants.

Additional information on the conditions of appointment, staffing and activities of the Department, together with application forms will be supplied upon request to the Secretary, Association of Universities of the British Commonwealth, 36 Gordon Square, London, W.C.1. Applications close on July 31, 1961.

BIOCHEMIST (BASIC GRADE). CANDIdates should hold a degree (preferably with honours) in chemistry or biochemistry, or an equivalent qualification. The person appointed will share in the routine work of the Department which receives specimens for unusual chemical investigations from many other hospitals, but there will also be opportunity for conducting original work. Salary according to Whitley scale commencing at £730 per annum (first- or second-class honours graduates).—Application, with the names of two referees, should be made within fourteen days to the Secretary, Lewisham Group Hospital Management Committee, Lewisham Hospital, S.E.13.

## SOUTHERN UNIVERSITIES NUCLEAR INSTITUTE

(Under the auspices of the Universities of Cape Town and Stellenbosch, Republic of South Africa)

Applications are invited for the post of **Chief Engineer** of the above Institute which will be built round a 5.5 MeV. Van de Graaff accelerator. The Chief Engineer will be responsible for the maintenance and operation of the Van de Graaff accelerator and other major equipment. He should have an all-round technical background in Nuclear Physics and Electronics, and is expected to participate in the technical development of the Research programme of the Institute. The successful applicant may be required to spend a short preliminary period at the factory of the manufacturers, the High-Voltage Engineering Corporation, Mass., U.S.A.

Fixed Salary: Within the range R.4,000 to R.5,000 (£2,000 to £2,500).

Applications, stating earliest date on which duties can be assumed, qualifications, at least two references, experience, present salary, and accompanied by a recent medical certificate must reach the Secretary, Southern Universities Nuclear Institute, c/o Merensky Institute for Physics, University of Stellenbosch, South Africa, by June 30, 1961. Further particulars, including membership of pension scheme, are available from the Secretary.

## UNIVERSITY OF BELFAST

The Senate of the Queen's University of Belfast invites applications for a Lectureship in Electrical Engineering from October 1, 1961. Salary range, £1,050 to £1,850 plus contributory pension rights under the F.S.S.U. Candidates should have experience in electrical measurement or measurement and control. Initial placing on the salary scale will depend on qualifications and experience. Applications should be received by June 30, 1961.

Further particulars may be obtained from G. R. Cowie, M.A., LL.B., J.P., Secretary.

## NEW ZEALAND

### ENTOMOLOGIST REQUIRED

Applications are invited from qualified Entomologists for an appointment with a progressive New Zealand company with extensive international associations and specializing in agricultural chemicals. This company is well established in the herbicide field as a result of its research and development programme. It is intended to expand this programme to include insecticides (horticultural and veterinary), fungicides, etc. The applicant should be capable of planning and implementing this research in close liaison with Government research departments. The commencing salary will be determined according to qualifications and experience. A superannuation scheme is available and some assistance in travelling expenses to New Zealand will be available.

Applications, giving full details of age, qualifications, experience, marital status, etc., should be forwarded to The Works Director, Ivon Watkins Ltd., P.O. Box 144, New Plymouth, New Zealand.

## UNIVERSITY OF LEEDS

### PROCTOR MEMORIAL FELLOWSHIP

Applications are invited for the Proctor Memorial Fellowship of a value not less than £700 a year. The Fellowship is tenable for one year in the first instance but the appointment may be renewed for a further period of not more than one year. The Fellow, who may be of any nationality, should be a science or technology graduate, with postgraduate research experience. He must devote the whole of his time to research on a subject pertaining to the leather or allied industries, in the Department of Leather Industries of the University of Leeds.

Applications, together with the names of three referees, should be sent to the Registrar, the University, Leeds 2 (from whom further particulars may be obtained), not later than July 28, 1961.

## THE ROYAL COLLEGE

### NAIROBI

Applications are invited for: (a) Senior Lectureship or Lectureship in Physics. Previous research experience (theoretical or experimental) in upper atmospheric physics and in palaeomagnetism or an allied subject would be valuable. (b) Lectureship in Geography. (c) Lectureship in Mathematics. Salary scales: Senior Lecturer, £1,950 by £75 to £2,475 per annum; Lecturer, £1,350 by £51 to £1,707 by £72 to £1,851 by £75 to £2,151 per annum, entry point determined by qualifications and experience. F.S.S.U. Child allowance £50 per annum per child (maximum £150 per annum). Passages for appointee and family (up to four adult passages) on appointment, termination and leave (once every two years). Rent according to quarters provided £60 to £114 per annum.

Detailed applications (six copies), naming three referees, by July 26, 1961, to Secretary, Inter-University Council for Higher Education Overseas, 29 Woburn Square, London, W.C.1, from whom further particulars may be obtained.

## UNIVERSITY OF GLASGOW

### LECTURESHIP IN COMPUTING LABORATORY

Applications are invited for a Lectureship in the Computing Laboratory, tenable from October 1, 1961. Salary scale: £1,050 to £1,850 per annum. F.S.S.U. and family allowance benefits. The principal equipment of the Laboratory is an English Electric DEUCE computer. Applicants should have experience in the use of digital computers, preferably in applications to crystallography or business calculations.

Applications (eight copies), should be lodged, not later than June 30, 1961, with the undersigned, from whom further particulars may be obtained.

ROBT. T. HUTCHESON,
Secretary of University Court.

## UNIVERSITY OF DUBLIN

### TRINITY COLLEGE
### JUNIOR LECTURER IN ORGANIC CHEMISTRY

Applications are invited for the post of Junior Lecturer in Organic Chemistry; duties to be taken up on September 21, 1961. Salary in the range £712 10s. by £47 10s. to £902 10s., with membership of the non-contributory superannuation and life assurance scheme, and with marriage and child allowances. £75 of the salary will be regarded as expenses.

Applications (four copies), giving full details of academic career and experience, and the names and addresses of three referees, should reach the Registrar, Trinity College, Dublin 2, from whom further particulars may be obtained, not later than July 3, 1961.

## BRITISH COUNCIL

IRAQ

UNIVERSITY OF BAGHDAD

Applications are invited for the following professorships and assistant professorships.

College of Medicine, Mosul, 1961/62: Histology, Physiology, Biology, Anatomy. 1962/63: Pathology, Pharmacology, Bacteriology and Parasitology.

College of Medicine, Baghdad, 1961/62: Bacteriology, Ophthalmology, Anaesthetics, Public Health and Social Medicine, Physiology, Gynaecology and Obstetrics, Paediatrics.

Duties similar to those in equivalent posts in U.K. universities. Candidates must have additional degrees to their qualifying degrees, with relevant teaching and research experience. Basic salary £1,980 to £3,700, according to qualifications and experience. Overseas allowance (maximum): £685 single, £1,125 married; a year. Children's and home education allowances. Free furnished accommodation. Installation grant. Employer's portion U.K. superannuation paid. Medical scheme. Contracts with Iraqi Ministry of Education and British Council for one year initially, renewable. Fares paid and for family, including home leave every two years and mid-tour passages for children in U.K. Secondment from home employment may be arranged.

Write, quoting N.7.Ni61), and enclosing stamped, addressed foolscap envelope, to Director, Recruitment Department, British Council, 65 Davies Street, London, W.1., for further particulars and application form to be returned within two weeks of receipt.

## BRADFORD INSTITUTE OF TECHNOLOGY

DEPARTMENT OF PHARMACY

Applications are invited for

RESEARCH FELLOWSHIPS AND RESEARCH ASSISTANTSHIPS IN PHARMACOGNOSY

Two posts are available, one of which is for work under the direction of Dr. J. M. Rowson, Head of the Department. Candidates should have a good honours degree pharmacy or allied subjects. Salary in accordance with the Burnham Technical Award for Assistant Grade B for Fellowships (£700 to £1,150 plus training and graduate allowances) and for Assistants Grade A for Assistantships (£520 to £1,000 plus allowances).

Further particulars and forms of application may be obtained from the Registrar (Dept. F), Bradford Institute of Technology, Bradford 7.

HENRY PATTEN,
Clerk to the Governors.

## LOUGHBOROUGH COLLEGE OF TECHNOLOGY

Applications are invited for a Lecturer to join the Metallurgy staff team. Candidates should be well qualified in metallurgy and should have had industrial or research experience of the properties and engineering applications of both metallic and non-metallic materials. Salary £1,370 rising to £1,550 per annum.

Further particulars and application form may be obtained from the Academic Registrar. (In reply please quote ref. 10/2/AE.)

APPLICATIONS ARE INVITED FOR THE position of Assistant Professor of Biology with specialization in Limnobiology. Ph.D. standing or its equivalent from a recognized University is essential. Salary will be in the range $7,000 to $8,500, depending upon qualifications and experience. Appointment dates from July 1, 1962. Duties at the University commence not later than September 1, 1962, and include undergraduate teaching in general biology and a programme of research and graduate teaching in Limnobiology. Facilities in this field are excellent.—Applications, including curriculum vitae, names of referees, and a recent photograph, should be addressed to Head of Department of Biology, University of Saskatchewan, Saskatoon, Saskatchewan, Canada.

A SENIOR TECHNICAL ADVISER IS required to initiate and develop (with the assistance of a large international organization) an advisory service in animal nutrition with particular reference to vitamins. A good honours degree or professional qualifications in science is essential, and experience in the field very desirable. Age about 30 to 35 years; to cover the whole of the United Kingdom but resident in London. Established personal connections with feed manufacturers and research stations a strong recommendation. Salary according to qualifications and experience. Excellent pension fund. A Junior Assistant is also required.—Apply Box No. 971, T. G. Scott and Son, Ltd., 1 Clement's Inn, London, W.C.2.


ICI

# A BOTANIST

## IS REQUIRED BY PLANT PROTECTION LIMITED

(A Subsidiary Company of Imperial Chemical Industries Limited)

at its research station at Jealott's Hill, near Bracknell, Berkshire. The vacancy is in the section working on herbicides and growth regulating chemicals.

Applicants should be male graduates in botany with good honours degrees and preferably postgraduate qualifications, and should not exceed 30 years of age.

Applications should be made in the first instance giving brief details only to the

**Staff Officer,**
**Plant Protection Ltd.,**
**Fernhurst, Haslemere, Surrey.**



## AUSTRALIA

***COMMONWEALTH SCIENTIFIC AND INDUSTRIAL RESEARCH ORGANIZATION***

# POST-DOCTORAL FELLOWSHIPS IN PROTEIN CHEMISTRY

The Organization's Division of Protein Chemistry, Melbourne, Victoria, invites applications from graduates in Chemistry or Physics for Post-Doctoral Fellowships. Applicants should have had research experience either in the protein field or with physical or chemical techniques which would find application in this field.

The Fellows selected will join a group of 25 research workers investigating various aspects of protein structure and chemistry. The protein research programme which has been developed by this group over the past twelve years provides an excellent opportunity for gaining experience in this field. A wide range of research equipment for chemical, physico chemical, biophysical and histological studies on proteins is available and a choice of projects relating to both fibrous and globular protein will be offered for selection.

The Fellowships are offered for a period of three years.

SALARY: Commensurate with qualifications and experience; minimum offered £A.1,750 per annum up to a maximum of £A.2,720 per annum. Salary for women will be £A.180 per annum less than corresponding rate for men.

Return fares paid. Further particulars of conditions, etc., supplied on application to: **Mr. E. J. Drake, Chief Scientific Liaison Officer, Australian Scientific Liaison Office, Africa House, Kingsway, London, W.C.2,**

*to whom applications (quoting Appointment No. 462/127), should be addressed by August 19, 1961.*


## UNIVERSITY OF NOTTINGHAM

RESEARCH ASSISTANT IN AGRICULTURAL CHEMISTRY

Applications are invited from graduates in agricultural chemistry, biochemistry or chemistry for appointment as Research Assistant to Professor E. G. Hallsworth at the School of Agriculture, Sutton Bonington, for work on the nutrition and biochemistry of the Leguminosae. There will be an opportunity for the appointee to write up part of the work for a higher degree of the University of Nottingham. Salary scale £550 by £50 to £700 per annum, the initial salary depending upon age, qualifications and experience.

Conditions of appointment and form of application, to be returned by July 8, from the Registrar.

## SOUTHEND-ON-SEA GENERAL HOSPITAL

PHYSICS TECHNICIAN (SENIOR GRADE)

Required in the Physics Department of the above hospital, the duties including work in the new radioactive isotope unit. Applicants must have had at least three years experience as a technician and must have passed the intermediate B.Sc. examination in physics or its equivalent. Previous experience in handling radioactive substances essential. Salary scale £710 by £25 (3) by £30 (4) to £905.

Applications, stating age, qualifications and previous experience, together with the names of two referees, are to be sent to the Secretary, General Hospital, Southend-on-Sea, as soon as possible.

## RESEARCH FELLOWSHIPS
in
GOVERNMENT SCIENTIFIC ESTABLISHMENTS

Tenable for three years

Value £1,325 to £1,640 per annum (Senior) and £910 to £1,220 per annum (Junior). A very wide range of topics in Physics, Mathematics, Chemistry, Engineering, Biology and other fields. Qualifications: normally first- or second-class honours degree; evidence of high standard of ability in research; and at least two years' postgraduate research experience (three years for Senior Fellowships). Those completing these periods of experience in 1961 may apply. F.S.S.U.

Write Civil Service Commission, 17 North Audley Street, London, W.1, for application form, quoting **S/5244/61**.

## IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY
DEPARTMENT OF MECHANICAL ENGINEERING

Lecturer required for Nuclear Power group. Applicants should be applied mathematicians with experience in numerical analysis and the use of digital computers for the solution of engineering problems. Salary in scale £1,050 by £50 to £1,400 by £75 to £1,550 (bar) by £75 to £1,850 per annum, plus £60 per annum London allowance, family allowances and F.S.S.U. membership.

Applications (in duplicate) to Dr. P. J. Grant, Department of Mechanical Engineering, Imperial College of Science and Technology, London, S.W.7, by July 31, 1961.

## CAMBRIDGE UNIVERSITY
LECTURESHIP IN MATHEMATICS

The Faculty of Mathematics intends to appoint a University Lecturer in Mathematical Statistics to take office on October 1, 1961. The appointment will be for three years in the first instance with the possibility of reappointment to the retiring age. The salary scale is £1,250 to £2,075, plus family allowances.

Applications, together with the names of two referees, should be sent to the Secretary of the Appointments Committee of the Faculty of Mathematics, the Arts School, Bene't Street, Cambridge, from whom further information may be obtained, and should reach him not later than July 12, 1961.

## UNIVERSITY OF GLASGOW
ASSISTANTSHIP IN ASTRONOMY

Applications are invited for an Assistantship in Astronomy. Salary scale: £800 to £950 per annum. Initial salary according to experience and qualifications. F.S.S.U. and family allowance benefits. Applicants should have a first- or second-class honours degree in astronomy, mathematics or physics and should preferably have an interest in radio astronomy. Facilities are available for research in theoretical astrophysics.

Applications (three copies), should be lodged, not later than July 7, 1961, with the undersigned, from whom further particulars may be obtained.

ROBT. T. HUTCHESON,
Secretary of University Court.

## UNIVERSITY OF MANCHESTER

Applications are invited from graduates for the post of Assistant Lecturer in Psychology. Candidates should have special interests in the problems of human engineering. Applications will be considered from candidates who intend to graduate in 1961. Salary on a scale £800 to £950 per annum with membership of the F.S.S.U. and Children's Allowance Scheme.

Applications should be sent not later than June 30, 1961, to the Registrar, the University, Manchester, 13, from whom forms of application and further particulars may be obtained.

RESEARCH ASSISTANT, OR TECHNICAL Assistant, required as soon as possible, mainly for work in Organic Chemistry and Chromatography. Salary in the range £500 to £800 per annum, with superannuation, according to qualifications and experience.—Apply to Professor G. A. D. Haslewood, Biochemistry and Chemistry Department, Guy's Hospital Medical School, London Bridge, S.E.1.

LIBRARIAN (TECHNICAL). LADY OVER 25 for classifying (U.D.C.) and cataloguing; should have taken Part I Registration or First Professional Examination and be able to type cards. Part-time worker might be suitable. Holidays honoured. Good working conditions, holidays and pay. 38½-hour week.—Please send details of education and experience to the Personnel Manager, The Plessey Company Limited, Ilford, Essex.

## UNIVERSITY OF ABERDEEN
RESEARCH FELLOWSHIP
AGRICULTURAL BIOCHEMISTRY

Applications invited for a Research Fellowship (Senior or Junior) for research on the Immunology of the Pituitary Gonadotrophic Hormones to be carried out in the Agricultural Biochemistry Division of the Department of Biological Chemistry. Previous experience of immunological methods desirable but not essential. The value of this Fellowship will be within the range £800 to £1,150 per annum with F.S.S.U.

Applications should be sent to the Secretary, the University, Aberdeen, from whom further particulars may be obtained, not later than July 7, 1961.

## UNIVERSITY OF ABERDEEN
DEPARTMENT OF CHILD HEALTH

Applications invited for the post of Lecturer in Child Health. Salary on scale £1,100 to £2,350 with placing according to qualifications and experience. F.S.S.U., child allowance and removal allowance.

Further particulars may be obtained from the Secretary, the University, Aberdeen, with whom applications (ten copies), should be lodged not later than August 16, 1961.

## BRITISH BAKING INDUSTRIES RESEARCH ASSOCIATION

Analyst, graduate or A.R.I.C., required as Scientific Officer for Analytical Laboratory. Duties will include research into analytical methods and the investigation of a wide range of problems associated with the Baking Industry. Some experience of food analysis would be an advantage.

Applicants should preferably be aged about 25 years. Salary according to qualifications and experience. The post is pensionable under F.S.S.U.

Applications, including details of age, qualifications, experience and the names of two referees, should be sent to:

**The Director of Research,**
**Baking Industries Research Station,**
**Chorleywood,**
**Herts.**

DIRECTORATE OF OVERSEAS GEOLOGICAL Surveys: Senior Scientific Officer. Pensionable post in Tolworth, Surrey, for man aged (normally) at least 26 on December 31, 1961. Qualifications: first- or second-class honours degree in geology or mining geology (or equivalent), or high professional attainment, and at least three years' appropriate postgraduate or other approved experience. Experience of geological mapping in overseas territories and of photogeological technique essential. Interim salary scale £1,392 to £1,714. Starting salary may be above minimum. Promotion prospects.—Write, Civil Service Commission, 17 North Audley Street, London, W.1, for application form, quoting **S/5326/61**. Closing date July 14, 1961.

WORCESTER FOUNDATION FOR EXPERIMENTAL Biology, U.S.A. Recent B.Sc. or M.Sc. Organic chemist for research work on synthesis from natural products. One-year appointment. Opportunity to make use of well-equipped spectroscopy department (NMR, IR, U-V and Optical Rotatory Dispersion).—For details contact: Mrs. Mabel S. Jacobsen, W.F.E.B., 222 Maple Avenue, Shrewsbury, Massachusetts, U.S.A.

INSTITUTE OF CANCER RESEARCH: Royal Cancer Hospital. Research Assistant required to assist in work on tissue transplantation at Pollards Wood Research Station, Chalfont St. Giles, Bucks. Candidates preferred with G.C.E. "A" level or higher qualification in biochemistry or biology. Salary on M.R.C. scales for Technical Officers according to age, qualifications and previous experience.—Apply with names of two referees to the Secretary, 33 Sumner Place, S.W.7, quoting ref. 301/B/61.

## UNIVERSITY OF LEEDS
DEPARTMENT OF PSYCHOLOGY

Applications are invited for appointment as Temporary Assistant Lecturer in the Department of Psychology for session 1961-62 only. Salary within the range £800 to £950 a year, according to age, qualifications and experience. Candidates should have a good graduate qualification in psychology and preferably some teaching experience in the subject.

Applications (three copies), stating date of birth, qualifications and experience, together with the names of three referees, should reach the Registrar, the University, Leeds, 2 (from whom further particulars may be obtained), not later than July 7, 1961.

## ST. THOMAS'S HOSPITAL MEDICAL SCHOOL

Applications are invited for the post of Assistant Lecturer in the Department of Biochemistry. The post will be tenable from October 1, 1961. Commencing salary, according to qualifications and experience, in the scale £950 to £1,150 per annum plus London allowance of £60. Membership of the F.S.S.U. and children's allowance scheme.

Applications, giving details of qualifications and the names of two referees, should be submitted by July 1, 1961, to the Dean, St. Thomas's Hospital Medical School, London, S.E.1, from whom further information may be obtained.

## LOUGHBOROUGH COLLEGE OF TECHNOLOGY
LEICESTERSHIRE
RESEARCH APPOINTMENTS

Applications are invited from those interested in undertaking research in: Electrical Engineering, Production Engineering, Mechanical Engineering, Civil Engineering, Chemical Engineering, Chemistry, Ergonomics, Liberal Studies, Industrial Fitness. Appointments may be made as appropriate in any of the following grades: Research Fellows, £750 per annum for three years; Research Scholars, £350 to £500 per annum for one year; Research Assistants, £520 to £1,000 per annum. Applicants should have a degree, Dip. Tech., or equivalent.

Application forms and other particulars from Academic Registrar, quoting reference 16/AF.

## BRISTOL COLLEGE OF SCIENCE AND TECHNOLOGY
ASHLEY DOWN, BRISTOL 7
DEPARTMENT OF CHEMISTRY AND BIOLOGY
READER IN ZOOLOGY

Applications invited for above appointment, being made in accordance with the planned development of the College. Candidates required to have had considerable experience of both teaching and research. Salary scale (at present under review) within range £1,800 to £2,100.

Application forms and details from the Registrar. Please quote ref. CST 61/25.

BACTERIOLOGIST WITH POSTGRADUate experience required to assist in a programme of research into enteric diseases of young farm animals, with especial reference to pigs, at the Animal Health Trust, Farm Livestock Research Centre, Stock, Essex. Salary within the scale £800 to £1,100; point of entry to be determined by age and experience. The post is superannuated under the F.S.S.U.—Further particulars can be obtained from the Scientific Director, Animal Health Trust, 14 Ashley Place, London, S.W.1.

MEDICAL RESEARCH COUNCIL LABORAtories, Carshalton, Surrey, require a Technical Officer (£920 to £1,260) or Junior Technical Officer (£410 to £860) to assist in biochemical research. Applicants should be over the age of 22 and have either a General Degree, H.N.C. in chemistry or the Advanced Certificate of the Institute of Biology. Experience in chromatographic and isotope techniques would be an advantage.—Applications, with details of education and experience, should be sent by July 31 to the Director, Toxicology Research Unit, M.R.C. Laboratories, Woodmansterne Road, Carshalton, Surrey.

RESEARCH ASSISTANT REQUIRED IN connection with insecticide research, to maintain insect colonies and assist with biochemical work. Graduate could register for higher degree. Salary £500 to £600 according to age and qualifications.—Apply to Dr. Busvine, London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.

**Pharmaceuticals Division**

Applications are invited from **YOUNG GRADUATES** (male or female) for an appointment in the Division's Research Laboratories. These are amongst the most up-to-date and best equipped in the world, situated in pleasant though not isolated rural surroundings at Alderley Park, between Macclesfield and Wilmslow, Cheshire.

The work is connected with toxicological investigations on synthetic drugs, and preferably, candidates should have a knowledge of Mammalian Hi··ology. Training will be given in Histopathology.

Applications with brief particulars, should be addressed to :

*THE DIVISION STAFF MANAGER*
**IMPERIAL CHEMICAL INDUSTRIES LIMITED**
**PHARMACEUTICALS DIVISION**
Fulshaw Hall, Wilmslow, Cheshire



## UNIVERSITY OF QUEENSLAND

***Reader • Senior Lecturer***
*and*
***Lecturer in Mathematics***

The University invites applications for three new posts in the Department of Mathematics. Applicants' special fields of interest may lie in Pure Mathematics, Applied Mathematics or Mathematical Statistics. The positions and salary ranges are:

| | | | |
|---|---|---|---|
| **READER** | **£A.2,960** | **by £A.60** | **to £A.3,200** |
| **SENIOR LECTURER** | **£A.2,520** | **by £A.70** | **to £A.2,870** |
| **LECTURER** | **£A.1,830** | **by £A.70** | **to £A.2,330** |

The qualifications for Lecturer are an Honours Degree in Mathematics and preferably some postgraduate study; for Senior Lecturer, experience in research; and for Reader, publication of significant contributions to Mathematics.

The University has recently planned a Computer Centre and a G E 225 computer is expected to be in operation within one year.

The successful applicants will be entitled to participate in the benefits available to the academic staff which include F.S.S.U. type Superannuation, Housing Assistance, Study Leave and Travel Grants.

Additional information about the positions and the staffing and activities of the Department, together with application forms will be supplied upon request to the Secretary, Association of Universities of the British Commonwealth, 36 Gordon Square, London, W.C.1.

Applications close, in Australia and London, on July 31, 1961.



## GRADUATES IN AGRICULTURE, SCIENCE, AND VETERINARY SCIENCE

required by

AN FORAS TALUNTAIS (The Agricultural Institute) for research on sheep husbandry, nutrition and related fields under its Animal Production Division at National Sheep Research Centre, Creagh, Ballinrobe, Co. Mayo. Salary and rating according to qualifications and experience.

(1) **SENIOR RESEARCH OFFICER, RESEARCH OFFICER or RESEARCH CADET**

At least one post. ESSENTIAL: Honours Degree in Agriculture, Science (majoring in Physiology) or Veterinary Science. DESIRABLE: Experience in animal nutrition and/or animal husbandry research.

(2) **RESEARCH OFFICER or RESEARCH CADET**

At least one post. ESSENTIAL: Honours Degree in Science (majoring in Chemistry or Biochemistry).

Further particulars and application forms from Director, An Foras Taluntais, 33 Merrion Road, Dublin, 4. Latest date for return of completed forms, July 14, 1961.



## WOOLWICH POLYTECHNIC
LONDON, S.E.18

Principal: Harold Heywood, D.Sc., Ph.D., A.C.G.I., Wh.Sch., M.I.Mech.E., M.I.Chem.E.

Applications invited for Research Assistantships in Physics from honours graduates. The Research Assistant will normally work for the Ph.D. (Internal) of the University of London. The post is tenable for two to three years, value £550 to £650 a year.

Particulars and application form from Clerk to Governors, to whom the application should be returned as soon as possible.

## UNIVERSITY OF NOTTINGHAM

Applications are invited for a Demonstratorship in Physics. Salary within the scale £550 by £25 to £600.

Conditions of appointment and form of application, to be returned as soon as possible, from the Registrar.

A SENIOR BIOCHEMIST (N.H.S. SALARY scale) is required for the development and application of advanced techniques for the analyses of steroids in body fluids. A knowledge of steroid biochemistry and of isotope techniques would be an advantage. The person appointed will work under the direction of the Regional Consultant in Steroid Biochemistry and in collaboration with the Steroid Research Unit at the Royal Infirmary, Glasgow.—Applications, giving details of age, qualifications and previous experience, together with the names of two referees, should be addressed to the Secretary and Treasurer, Board of Management for Glasgow Royal Infirmary and Associated Hospitals, 84 Castle Street, Glasgow, C.4, from whom further details may be obtained.

DURHAM UNIVERSITY COMPUTING Laboratory. Applications are invited from graduates with research experience for a post of Research Assistant in the Computing Laboratory, to commence on October 1, 1961, or a later date to be arranged. Applicants should have an interest in numerical analysis or in some field of application of automatic computers. The initial salary will be fixed in accordance with age and experience within the scale £850 to £1,350, with F.S.S.U. and family allowance.—Applications (three copies), should be sent to the Director, University Computing Laboratory, 1 Kensington Terrace, Newcastle upon Tyne, 2, by July 31, 1961, from whom further particulars may be obtained.

For an important Group of Biological, chemical-biological Laboratories, an outstanding firm in the field of nutritional products requires :

## *A Director of the Scientific Department*

with full responsibility in research promotion and co-ordination of various Departments.

NECESSARY CONDITIONS:

- an excellent formation and a striking scientific personality, tested by Curriculum and publications ;
- an extensive experience in the management of one or more Research Departments ;
- a clear ascendancy and authority, along with the ability of earning the collaboration of subordinates.

FORESEEN:

A membership in the Managing Board of the Industry which the Laboratories belong to, and a high-level salary.

**Write to: PUBBLIMAN–Casella 179 M.–Milano (Italy)**

## COUNTY LABORATORIES LIMITED

Manufacturers of Brylcreem, Silvikrin, Macleans Toothpaste and many other well-known toiletry preparations require for their Product Research Laboratory

## SENIOR BIOCHEMIST

Honours Graduate to lead research on the biochemistry and physiology of skin and hair.

Excellent working conditions in new laboratories. Profit participation and non-contributory pension schemes in operation.

Apply in writing to Personnel Manager, County Laboratories Limited, Beecham House West, Great West Road, Brentford, Middlesex.

### UNIVERSITY COLLEGE OF THE WEST INDIES

Applications are invited for: (i) Senior Lecturer in Civil Engineering from candidates with interest in hydraulics. (ii) Senior Lecturer in Electrical Engineering from candidates with interest in electronics. (iii) Lecturer in Civil Engineering from candidates with interest in surveying. Salary scales: Senior Lecturer, £1,500 by £75 to £2,425 per annum ; Lecturer, £1,050 by £50 to £1,400 by £75 to £1,850 per annum, plus local allowance of £250 per annum (pensionable). Entry point according to qualifications and experience but in case of Lecturers below merit bar consideration is given to age. Child allowance. F.S.S.U. Unfurnished accommodation at rental of 10 per cent of basic salary. Up to five full passages on appointment, normal termination and triennial study leave. Duties to be assumed as soon as possible.

Detailed applications (six copies), naming three referees, by July 15, 1961, to Secretary, Inter-University Council for Higher Education Overseas, 29 Woburn Square, London, W.C.1, from whom further particulars may be obtained.

R.N. COLLEGE, GREENWICH, LONDON, S.E.10. Post for Senior Lecturer or Lecturer in Applied Mechanics available September, 1961. Candidates (male) must be British and possess an appropriate honours degree. Duties include lecturing and conducting laboratory work to degree standard and postgraduate teaching. Excellent research facilities. Appointment as Senior Lecturer (£1,392 to £1,714) or Lecturer (£773 to £1,267) according to age, qualifications and experience. Starting salary above minimum may be authorized. Posts carry F.S.S.U. benefits. Single accommodation available.—Particulars and application forms from Director (P), Education Department, Admiralty, London, S.W.1. Closing date for applications July 10, 1961.

THE UNIVERSITY OF SUSSEX. APPLICATIONS are invited for the Chair of Mathematics from 1962. The salary will be not less than £2,600 per annum plus family allowance and F.S.S.U. benefits.—Further particulars may be obtained from the Registrar, University College of Sussex, Stanmer House, Stanmer, Brighton, to whom applications should be sent by July 15, 1961.

### MONASH UNIVERSITY

Victoria, Australia

NEW ACADEMIC POSITIONS

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Senior Lecturers: £A.2,480 to £A.2,950 (if medically qualified: £A.2,600 to £A.3,250)
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Full information on application procedure, conditions of appointment, superannuation, travel and removal allowances, study leave and housing is available from the Secretary of the Association of Universities of the British Commonwealth, 36 Gordon Square, London, W.C.1, or the Registrar of the University, P.O. Box 92, Clayton, Victoria, Australia.

Closing date: Applications close with the Registrar of the University on July 31, 1961.

F. H. JOHNSON,
Registrar.

### UNIVERSITY OF SHEFFIELD

Applications are invited for a post of Junior Research Fellow in Pure Mathematics to begin duties on October 1, 1961. Salary £625 per annum. The appointment will be for one year in the first instance and will be renewable.

Applications (three copies), with the names and addresses of two referees, should reach the Registrar, from whom further particulars may be obtained, by July 1, 1961.

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Further particulars and forms of application may be obtained from the Registrar (Dept. F.), Bradford Institute of Technology, Bradford 7.

HENRY PATTEN,
Clerk to the Governors.

### BATTERSEA COLLEGE OF TECHNOLOGY

LONDON, S.W.11

Applications are invited from honours graduates of a British University for a Lectureship or Assistant Lectureship in Mathematics with special qualifications in numerical analysis. Salary: Lecturer, £1,408 by £35 to £1,601; Assistant Lecturer within the range £950 to £1,486; less statutory deductions.

Further particulars from the Clerk to the Governing Body, by whom applications should be received not later than July 1, 1961.

### AUSTRALIA

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## PASTURE PHYSIOLOGIST

The Organization's Division of Plant Industry, Canberra, A.C.T., invites applications from Honours graduates in Science or Agricultural Science with some years relevant post-graduate research experience and a background in ecology and/or plant physiology for the position of Pasture Physiologist at its **Regional Pastoral Laboratory, Deniliquin, N.S.W.**

The appointee will be required to study the physiology of pasture species in grazed swards; not only with the objective of producing pasture for animals economically, but also to elucidate the relationships between vegetative and floral development, particularly as they are affected by the grazing animal. These studies will be closely integrated with current investigations on the energetics of light exploitation by the pasture canopy and the production of species in irrigated swards.

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Mr. E. J. Drake, Chief Scientific Liaison Officer, Australian Scientific Liaison Office, Africa House, Kingsway, London, W.C.2,

to whom applications (quoting Appointment No. 132/105) should be addressed by July 29, 1961.

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BODLEIAN LIBRARY. THE LIBRARIAN invites applications for two graduate posts at the Radcliffe Science Library (a dependent library of the Bodleian) on a salary scale of £800 by £50 to £1,400 (bar) by £75 to £1,625. Candidates should have a good honours degree and preferably some relevant library experience. Preference will be given to candidates having a science degree.—Applications (six copies), stating age, qualifications and experience, and giving the names of two referees, should be submitted to the Librarian, Bodleian Library, Oxford, by July 15.

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## GRANTS & SCHOLARSHIPS

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The Mental Health Research Fund awards annually a Travelling Fellowship open to Non-medical Research Students intending to work in a field relevant to mental illness such as Neurophysiology, Neurochemistry, Pharmacology, Psychology, Sociology, etc. The Fellowship, which is additional to the Fellowship open to medical students, provides travelling expenses and full subsistence in a University or other Department abroad for up to six months. Applicants should generally be in the first five years after taking their B.A. or B.Sc. degree. In support of their applications they should submit an essay (length about 5,000 words) on some topic of their own choosing with clear relevance to research in mental illness. Before writing the essay the candidate should submit his full title to the Secretary for approval, at the address below. The final selection will be made by interview combined with consideration of the candidate's academic record.

Completed essays should be sent in triplicate, together with a brief curriculum vitae, to the Secretary, Research Committee, Mental Health Research Fund, 39 Queen Anne Street, London, W.1 (Telephone WELbeck 1272), before March 1, 1962.

### THE ROYAL SOCIETY

GOVERNMENT GRANT FOR SCIENTIFIC INVESTIGATIONS

Applications for grants from the second allotment of the Government Grant for Scientific Investigations for the year 1961, should be made as soon as possible on forms of application to be obtained from the Assistant Secretary of the Royal Society, Burlington House, London, W.1. No application can be considered which is received later than July 31, 1961.

Applicants must be of British nationality, resident in Great Britain or Northern Ireland. Grants may be made for purposes in connexion with the promotion and support of research in pure science other than for personal maintenance or payment of stipends; for the assistance of scientific expeditions and collections; but not in aid of scientific publications.

### UNIVERSITY OF SHEFFIELD

IMPERIAL CHEMICAL INDUSTRIES RESEARCH FELLOWSHIP

Applications are invited for an Imperial Chemical Industries Fellowship tenable at the University of Sheffield. The Fellowship may be awarded for the purpose of carrying out original research in chemistry, physics, engineering (including chemical engineering), metallurgy, pharmacology, or related subjects, and will be tenable from October 1, 1961, or as soon as possible thereafter. Save in exceptional circumstances the Fellow will be required to carry out the whole of his research work in Sheffield. Applicants should preferably hold the degree of Ph.D., or have equivalent research experience. The annual stipend of a Fellow will depend upon age, qualifications and experience but will be within the range £800 to £1,100, together with F.S.S.U. provision. The Fellowship will be tenable for a period to be decided, but not exceeding three years in all.

Applications (eight copies), stating age, details of career and qualifications, publications and an outline of the proposed research, together with the names of two referees, should be sent, not later than July 15, 1961, to the Registrar, the University, Sheffield 10, from whom further inquiries may be made.

### UNIVERSITY COLLEGE OF NORTH STAFFORDSHIRE

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Students wishing to attend the course should write to the Registrar before August 31, 1961. Students attending the course will be eligible to apply for D.S.I.R. Advanced Course Studentships.


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Further information and application forms can be obtained from the Secretary to the Department.


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K. Durham, the editor, is a member of the Research Department, Unilever, Ltd., Port Sunlight, as are two other contributors, H. E. Garrett and T. G. Jones. A. S. C. Lawrence is in the Department of Chemistry at the University of Sheffield and D. G. Stevenson is on the staff of the Atomic Weapons Research Establishment at Aldermaston.

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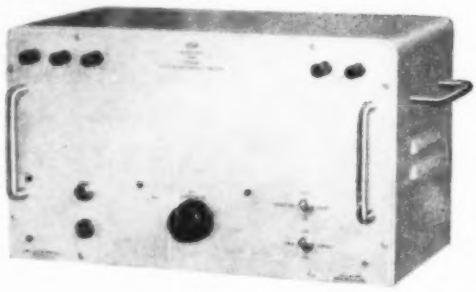

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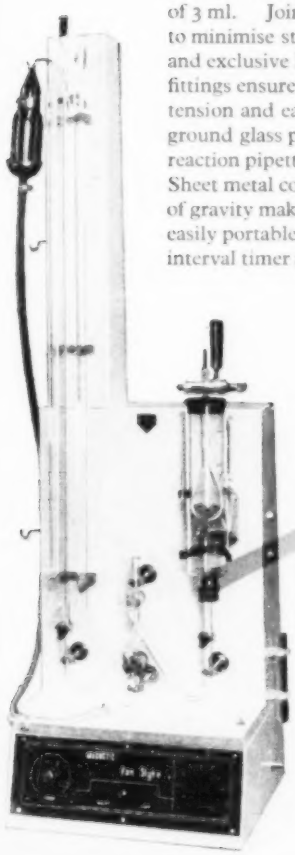

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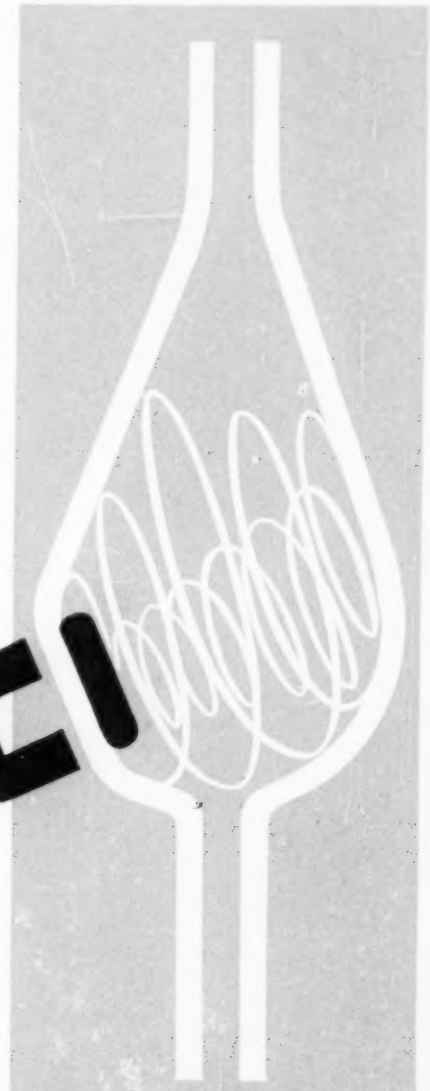

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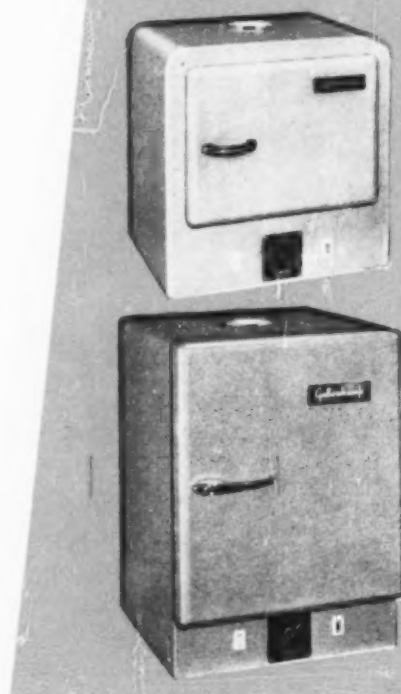

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